

Supplementary appendix to

Model-estimated effectiveness of single dose 9-valent HPV vaccination for HIV-positive and HIV-negative females in South Africa

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General Overview:

This mathematical model is designed to study the impact of HPV vaccination while accounting for HIV infection dynamics and HIV disease progression by CD4 count and antiretroviral therapy (ART). We constructed a model that simulates heterosexual HIV and HPV transmission and is parameterized to KwaZulu-Natal, South Africa (KZN), a region with high HIV prevalence. The model reproduces population-level dynamics and stratifies the population by age, gender, and sexual risk. We structure the model to incorporate ART scale-up targeted to HIV-positive persons by CD4+ T-cell (CD4) count.

The model begins in 1975 with an initial prevalence of HIV of 0.18% and 0.16% among males and females respectively. By 1985, the model population attains a size and demographic distribution reflecting that of KZN in 1985 (1, 2). The population dynamics are governed by a system of differential equations that are solved in MATLAB using a 4th-order Runge-Kutta method. The model iterates in two-month intervals from 1975 to 2100.

I. Technical Specifications

HIV Natural History:

The natural history of HIV infection is modeled in stages defined by CD4 count and viral load as shown in Figure S1. When a person becomes HIV-infected, s/he enters the acute stage characterized by a short duration and high probability of HIV transmission. The person then progresses through stages of CD4 count and viral load at rates ν^d and ω^v , respectively, where d represents the current CD4 count and v represents the current viral load. The parameters ν^d and ω^v are based on an analysis of disease progression using data from the Partners HSV/HIV and Partners PrEP studies. The average life expectancy from infection to death for untreated persons is 10.7 years.

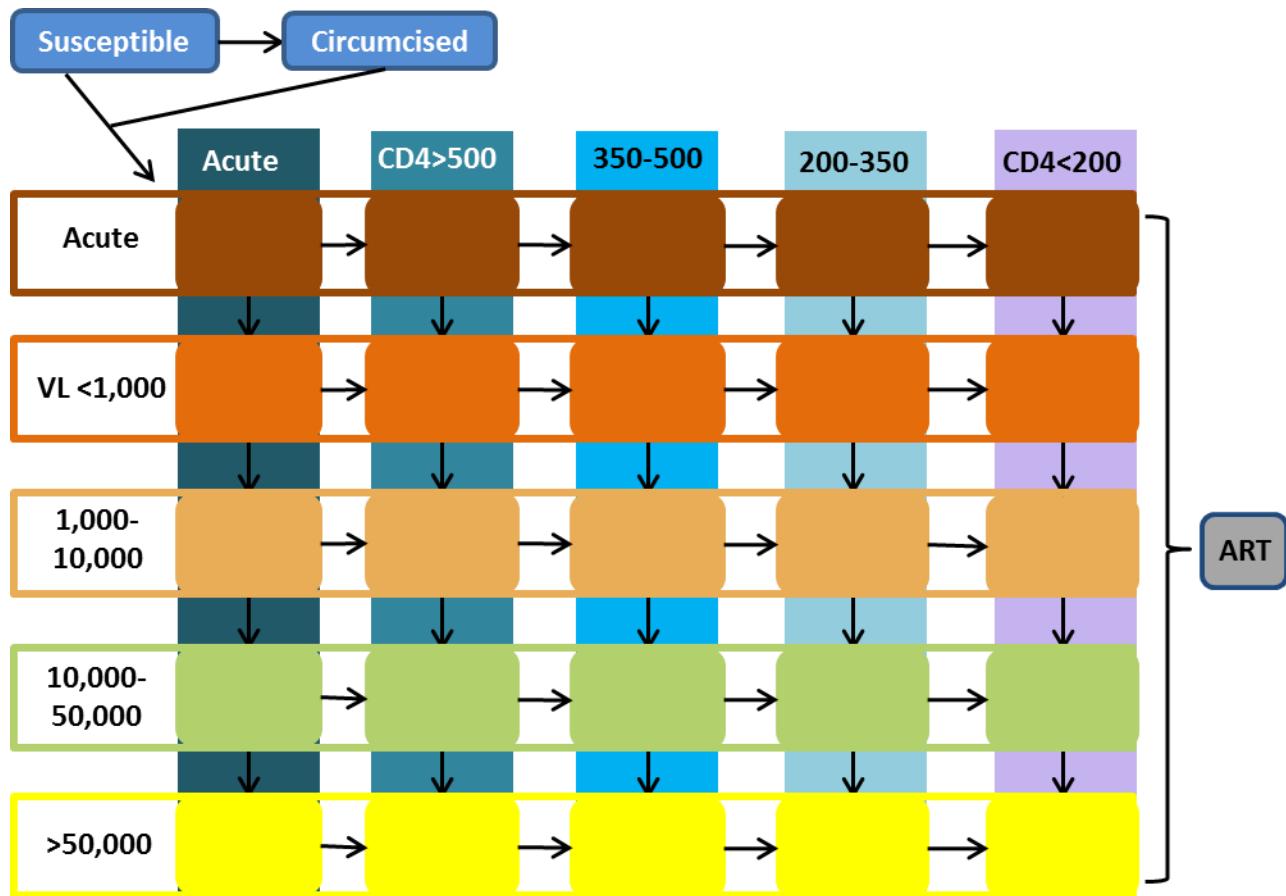


Figure S1. Model transition diagram. A diagram of the natural history of HIV infection. All movement is in one direction except for enrollment in and dropout from interventions from ART.

Ordinary Differential Equations:

The model simulates a population from ages 0 to 79 in five-year age-groups, capturing vertical transmission and aging. The system of differential equations describes the states $X_{a,r}^{g,d,v}(t)$ with the following indices:

- g refers to gender
 $g = 0$ for males; $g = 1$ for females
- d refers to disease state defined by CD4 cell count, and treatment and circumcision status
 $d = 0$ for HIV-negative; $d = 1$ for acute infection; $d = 2$ for CD4 > 500 cells/ μ L; $d = 3$ for CD4 500-350 cells/ μ L; $d = 4$ for CD4 350-200 cells/ μ L; $d = 5$ for CD4 < 200 cells/ μ L; $d = 6$

- for HIV-negative, circumcised, and no PrEP; $d = 7$ for HIV-negative, circumcised, and on PrEP; $d = 8$ for HIV-negative, uncircumcised, and on PrEP; $d = 9$ for HIV-positive on ART
- v refers to disease state defined by viral load

$v = 0$ for HIV-negative; $v = 1$ for acute infection; $v = 2$ for VL<1,000 copies/mL; $v = 3$ for VL 1,000-10,000 copies/mL; $v = 4$ for VL 10,000-50,000 copies/mL; $v = 5$ for VL>50,000 copies/mL; $v = 6$ for HIV-positive and on ART
 - a refers to age group

$a = 0$ for ages 0 to 4; $a = 1$ for ages 5 to 9; ... ; $a = 15$ for ages 75 to 79
 - r refers to sexual risk group defined by number of sexual partnerships per year

$r = 0$ for low risk; $r = 1$ for medium risk; $r = 2$ for high risk

The differential equations for the nine HIV disease states are:

$$\begin{aligned}
 \frac{dX_{a,r}^{g,0,0}(t)}{dt} &= b_{r,0}^{g,0}(t) + \sigma_{a,r}^{g,0} X_{a,r}^{g,7,0}(t) - (\mu_a^g + \psi_3 \lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)) X_{a,r}^{g,0,0}(t) \\
 \frac{dX_{a,r}^{g,1,v}(t)}{dt} &= b_{r,0}^{g,1}(t) + \lambda_{a,r}^{g,0} X_{a,r}^{g,0,0}(t) + \psi_3 \psi_0 \lambda_{a,r}^{1,0}(t) X_{a,r}^{1,6,v}(t) + \psi_3 \psi_0 \psi_1 \lambda_{a,r}^{1,1}(t) X_{a,r}^{1,7,0}(t) \\
 &\quad + \psi_3 \psi_1 \lambda_{a,r}^{g,1}(t) X_{a,r}^{g,9,6}(t) + \sigma_{a,r}^{g,1}(t) X_{a,r}^{g,9,6} - (\mu_a^g + \alpha_a^{g,1} + v_1 + \pi_{a,r}^{g,1,v}(t)) X_{a,r}^{g,1,v}(t) \\
 \frac{dX_{a,r}^{g,2,v}(t)}{dt} &= (v_1 + \omega_{v-1}) X_{a,r}^{g,1,v}(t) + \sigma_{a,r}^{g,2} X_{a,r}^{g,9,6}(t) - (\mu_a^g + \alpha_a^{g,2} + v_2 + \omega_v + \pi_{a,r}^{g,2,v}(t)) X_{a,r}^{g,2,v}(t) \\
 \frac{dX_{a,r}^{g,3,v}(t)}{dt} &= (v_2 + \omega_{v-1}) X_{a,r}^{g,2,v}(t) + \sigma_{a,r}^{g,3} X_{a,r}^{g,9,6}(t) - (\mu_a^g + \alpha_a^{g,3} + v_3 + \omega_v + \pi_{a,r}^{g,3,v}(t)) X_{a,r}^{g,3,v}(t) \\
 \frac{dX_{a,r}^{g,4,v}(t)}{dt} &= (v_3 + \omega_{v-1}) X_{a,r}^{g,3,v}(t) + \sigma_{a,r}^{g,4} X_{a,r}^{g,9,6}(t) - (\mu_a^g + \alpha_a^{g,4} + v_4 + \omega_v + \pi_{a,r}^{g,4,v}(t)) X_{a,r}^{g,4,v}(t) \\
 \frac{dX_{a,r}^{g,5,v}(t)}{dt} &= (v_4 + \omega_{v-1}) X_{a,r}^{g,4,v}(t) + \sigma_{a,r}^{g,5} X_{a,r}^{g,9,6}(t) - (\mu_a^g + \alpha_a^{g,5} + v_5 + \omega_v + \pi_{a,r}^{g,5,v}(t)) X_{a,r}^{g,5,v}(t) \\
 \frac{dX_{a,r}^{g,6,0}(t)}{dt} &= b_{r,1}^{g,0}(t) + \sigma_{a,r}^{g,0} X_{a,r}^{g,6,0}(t) - (\mu_a^g + \psi_3 \psi_0 \lambda_{a,r}^{g,0}(t) + \pi_{a,r}^{g,0,0}(t)) X_{a,r}^{g,6,0}(t) \\
 \frac{dX_{a,r}^{g,7,0}(t)}{dt} &= \pi_{a,r}^{g,0,0}(t) X_{a,r}^{g,5,0}(t) - (\sigma_{a,r}^{g,0} + \mu_a^g + \psi_3 \psi_0 \psi_1 \lambda_{a,r}^{g,1}(t)) X_{a,r}^{g,7,0}(t)
 \end{aligned}$$

$$\frac{dX_{a,r}^{g,8,0}(t)}{dt} = \pi_{a,r}^{g,0,0}(t)X_{a,r}^{g,0,0}(t) - (\sigma_{a,r}^{g,0} + \mu_a^g + \psi_3\psi_1\lambda_{a,r}^{g,1}(t))X_{a,r}^{g,8,0}(t)$$

$$\frac{dX_{a,r}^{g,9,6}(t)}{dt} = \sum_{v=1}^5 \sum_{d=1}^5 [\pi_{a,r}^{g,d,v}(t)X_{a,r}^{g,d,v}(t) - (\sigma_{a,r}^{g,d} + \mu_a^g)X_{a,r}^{g,9,6}(t)]$$

The equation variables are:

$b_{r,c}^{g,d}(t)$	The number of births that are HIV-negative ($d = 0$), HIV-positive ($d = 1$), uncircumcised ($c = 0$), or circumcised ($c = 1$)
$\sigma_{a,r}^{g,d}$	The dropout rate from PrEP ($d = 0$) or ART ($d = 1, \dots, 5$)
μ_a^g	The background mortality
$\lambda_{a,r}^{g,d}(t)$	The force of infection for HIV-negative persons on PrEP ($d = 1$) or off PrEP ($d = 0$)
$\pi_{a,r}^{g,d,v}(t)$	The coverage of PrEP ($d = 0$), ART ($d = 1, \dots, 5$), circumcision ($d = 6$), condom use among HIV-negative persons ($d = 7$), condom use among PrEP users ($d = 8$), and condom use among ART users ($d = 9$)
$\alpha_a^{g,d}$	The HIV-associated mortality
v_d	The rate of progressing from CD4 state d to $d + 1$
ω_d	The rate of progressing from VL state v to $v + 1$
ψ_d	The reduction in HIV transmission due to circumcision ($d = 0$), PrEP ($d = 1$), ART ($d = 2$), or condom use ($d = 3$)

HPV Natural History

The system of differential equations describes the states $X_{a,r}^{g,d,v,h,s}(t)$ with the following indices:

- g refers to gender

$g = 0$ for males; $g = 1$ for females

- d refers to disease state defined by CD4 cell count, and treatment and circumcision status

$d = 0$ for HIV-negative; $d = 1$ for acute infection; $d = 2$ for CD4 >500 cells/ μ L; $d = 3$ for

CD4 500–350 cells/ μ L; $d = 4$ for CD4 350–200 cells/ μ L; $d = 5$ for CD4 <200 cells/ μ L; $d = 6$

for HIV-negative, circumcised, and no PrEP; $d = 7$ for HIV-negative, circumcised, and on

PrEP; $d = 8$ for HIV-negative, uncircumcised, and on PrEP; $d = 9$ for HIV-positive on ART

- v refers to disease state defined by viral load

$v = 0$ for HIV-negative; $v = 1$ for acute infection; $v = 2$ for VL<1,000 copies/mL; $v = 3$ for VL 1,000-10,000 copies/mL; $v = 4$ for VL 10,000-50,000 copies/mL; $v = 5$ for VL>50,000 copies/mL; $v = 6$ for HIV-positive and on ART

- a refers to age group

$a = 0$ for ages 0 to 4; $a = 1$ for ages 5 to 9; ... ; $a = 15$ for ages 75 to 79

- r refers to sexual risk group defined by number of sexual partnerships per year
- $r = 0$ for low risk; $r = 1$ for medium risk; $r = 2$ for high risk
- $h = 0$ for HPV-negative , $h = 1$ for HPV=16/18 , $h = 2$ for 4v-vaccine oncogenic types; $h = 3$ for non-vaccine oncogenic types
- s refers to HPV disease state; 0 = No precancer (if $h = 0$) , infected (if $h \geq 1$); 1 = CIN1 ; 2 = CIN2; 3 = CIN3; 4 = Cervical Cancer (Local); 5 = Cervical Cancer (Regional); 6 = Cervical Cancer (Distant); 7 = Immune; 8 = Vaccinated

The differential equations for the HPV disease states are:

$$\frac{dX_{a,r}^{g,d,v,0,0}(t)}{dt} = \underline{\chi}_{0,7}^d r_a X_{a,r}^{g,d,v,1,7} - \left(\kappa_d \lambda_{HPV,a,r}^{g,d,h}(t) + V_a \cdot u(t - t_v) \right) X_{a,r}^{g,d,v,0,0}(t)$$

For $h \geq 1$

$$\begin{aligned} \frac{dX_{a,r}^{g,d,v,h,0}(t)}{dt} &= \kappa_d [\lambda_{HPV,a,r}^{g,d,h}(t) X_{a,r}^{g,d,v,0,0}(t) + \xi_a \lambda_{HPV,a,r}^{g,d,h}(t) X_{a,r}^{g,d,v,1,7} \\ &\quad + \phi_V(a) \lambda_{HPV,a,r}^{g,d,h}(t) X_{a,r}^{g,d,v,1,8} u(t - t_v)] + \underline{\chi}_{0,1}^d k_{0,1}^{a,h} X_{a,r}^{g,d,v,1,1} - (\Pi_{1,0}^d k_{1,0}^{a,h} \\ &\quad + \underline{\chi}_{0,0}^d 3^{a,h}) X_{a,r}^{g,d,v,1,0} \end{aligned}$$

$$\frac{dX_{a,r}^{g,d,v,h,1}(t)}{dt} = \Pi_{1,0}^d k_{1,0}^{a,h} X_{a,r}^{g,d,v,1,0} + \underline{\chi}_{1,2}^d k_{1,2}^{a,h} X_{a,r}^{g,d,v,1,2} - (\Pi_{2,1}^d k_{2,1}^{a,h} + \underline{\chi}_{0,1}^d k_{0,1}^{a,h}) X_{a,r}^{g,d,v,1,1}$$

$$\frac{dX_{a,r}^{g,d,v,h,2}(t)}{dt} = \Pi_{2,1}^d k_{2,1}^{a,h} X_{a,r}^{g,d,v,1,1} + \underline{\chi}_{2,3}^d k_{2,3}^{a,h} X_{a,r}^{g,d,v,1,3} - (\Pi_{3,2}^d k_{3,2}^{a,h} + \underline{\chi}_{1,2}^d k_{1,2}^{a,h}) X_{a,r}^{g,d,v,1,2}$$

$$\begin{aligned}
\frac{dX_{a,r}^{g,d,v,1,3}(t)}{dt} &= \mathfrak{N}_{3,2}^d k_{3,2}^{a,h} X_{a,r}^{g,d,v,1,2} - (k_{4,3}^{a,h} + \mathfrak{k}_{2,3}^d k_{2,3}^{a,h}) X_{a,r}^{g,d,v,1,3} \\
\frac{dX_{a,r}^{g,d,v,h,4}(t)}{dt} &= k_{4,3}^{a,h} X_{a,r}^{g,d,v,1,3} - (k_{5,4}^{a,h} + \zeta_4) X_{a,r}^{g,d,v,1,4} \\
\frac{dX_{a,r}^{g,d,v,h,5}(t)}{dt} &= k_{5,4}^{a,h} X_{a,r}^{g,d,v,1,4} - (k_{6,5}^{a,h} + \zeta_5) X_{a,r}^{g,d,v,1,5} \\
\frac{dX_{a,r}^{g,d,v,h,6}(t)}{dt} &= k_{6,5}^{a,h} X_{a,r}^{g,d,v,1,5} - \zeta_6 X_{a,r}^{g,d,v,1,6} \\
\frac{dX_{a,r}^{g,d,v,h,7}(t)}{dt} &= \mathfrak{z}_{0,0}^d z_{0,0}^{a,h} X_{a,r}^{g,d,v,1,0} - (\mathfrak{z}_{0,7}^d r_a + \mathfrak{z}_d \xi_a \lambda_{HPV_{a,r}}^{g,d,h}(t)) X_{a,r}^{g,d,v,1,7} \\
\frac{dX_{a,r}^{g,d,v,h,8}(t)}{dt} &= [V_a \cdot X_{a,r}^{g,d,v,0,0}(t) - \mathfrak{z}_d \phi_V(a) \lambda_{HPV_{a,r}}^{g,d,h}(t) X_{a,r}^{g,d,v,1,8}] u(t - t_v)
\end{aligned}$$

The equation variables are:

$\lambda_{HPV_{a,r}}^{g,d,v}(t)$	The force of infection for HPV-negative persons
\mathfrak{z}_d	HPV acquisition risk multiplier for HIV-positive individuals with CD4 count d
ξ_a	HPV acquisition risk reduction multiplier for individuals with natural HPV immunity
$\phi_V(a)$	HPV acquisition risk reduction multiplier for individuals vaccinated against HPV
$k_{s',s}^{a,h}$	Rate of progressing from HPV/CIN state s to s' for HPV type h
$z^{a,h}$	Rate of progressing from HPV infected to natural immunity by age a and HPV type h
ζ_s	Cervical cancer-associated mortality for persons at stage s
r_a	Rate of waning natural immunity
$\mathfrak{N}_{s',s}^d$	Progression rate multiplier from HPV/CIN stage s to s' for HIV-positive individuals with CD4 count/HIV status d
$\mathfrak{z}_{s,s'}^d$	Regression rate multiplier from HPV/CIN stage s' to s for HIV-positive individuals with CD4 count/HIV status d
t_v	The year that vaccination begins
V_a	Vaccination rate by age
$u(t - t_v)$	The Heaviside step function

Demography:

At each time step, the force of infection and the number of births are calculated and then used to evaluate the differential equations along with mortality and disease progression. The numbers of incident infections, HIV-related deaths, and individuals entering $CD4 \leq 200$ cells/ μL are also calculated.

Births:

The number of births, $b_{r,c}^{g,d}(t)$, determines how many newborns enter the population of gender g , disease state d , sexual risk group r , and circumcision status c ($c = 0$ for uncircumcised; $c = 1$ for circumcised males). For simplicity, we assume only neonatal circumcision (the circumcision level is increased over time such that 10% of males are circumcised by 2013, as currently observed in KZN and shown in Figure S2 (3, 4)), that infected births enter the acute stage, and that women age 15–49 give birth. Fertility rates are stratified by age and stage of disease. Births from uninfected mothers, $bS(t)$, and from HIV-positive mothers, $bI(t)$, are:

$$bS(t) = \sum_{a=3}^9 \sum_{r=0}^2 [\gamma_a^0 X_{a,r}^{1,0,0}(t) + \gamma_a^9 X_{a,r}^{1,9,6}(t)]$$

$$bI(t) = \sum_{a=3}^9 \sum_{r=0}^2 \sum_{d=1}^5 \sum_{v=1}^5 \gamma_a^d X_{a,r}^{1,d,v}(t) + \sum_{a=3}^9 \sum_{r=0}^2 \gamma_a^9 X_{a,r}^{1,9,6}(t)$$

HIV-negative births for uncircumcised males, $b_{r,0}^{0,0}(t)$, are:

$$b_{r,0}^{0,0}(t) = 0.5 * \phi_{0,r}^{0,0} * (bS(t) + (1 - \eta(t))bI(t)) * (1 - \pi_{0,r}^{1,5}(t))$$

HIV-negative births for circumcised males, $b_{r,1}^{0,0}(t)$, are:

$$b_{r,1}^{0,0}(t) = 0.5 * \phi_{0,r}^{0,0} * (bS(t) + (1 - \eta(t))bI(t)) * \pi_{0,r}^{1,5}(t)$$

HIV-negative births for females, $b_{r,0}^{1,0}(t)$, are:

$$b_{r,1}^{1,0}(t) = 0.5 * \phi_{0,r}^{1,0} * (bS(t) + (1 - \eta(t))bI(t))$$

HIV-positive births for males and females, $b_{r,0}^{g,1}(t)$, are:

$$b_{r,0}^{g,1}(t) = 0.5 * \phi_{0,r}^{g,0} * \eta(t)bI(t)$$

The equation variables are:

$\phi_{a,r}^{g,d}$	The proportion of individuals in age a , gender g , and treatment status d ($d = 0$, no treatment; $d = 1$, PrEP; $d = 2$, ART) that is born into sexual risk group r
$\eta(t)$	The proportion of births from HIV-positive females that result in vertical transmission
$\pi_{0,r}^{1,5}(t)$	The proportion of HIV-negative males that is circumcised at birth

$$\gamma_a^d \quad \text{The annual fertility rate for females by age and disease state}$$

Each birth is multiplied by 0.5 to reflect an assumed gender ratio at birth of 1:1. The proportion of births from HIV-positive mothers that result in infection, $\eta(t)$, decreases linearly from 34% in 2004 to 20.2% in 2005, then to 7.1% in 2008 (5-7). The proportion of circumcised HIV-negative males, $\pi_{0,r}^{1,5}(t)$, remains at 10% from 1990 to 2013 (3).

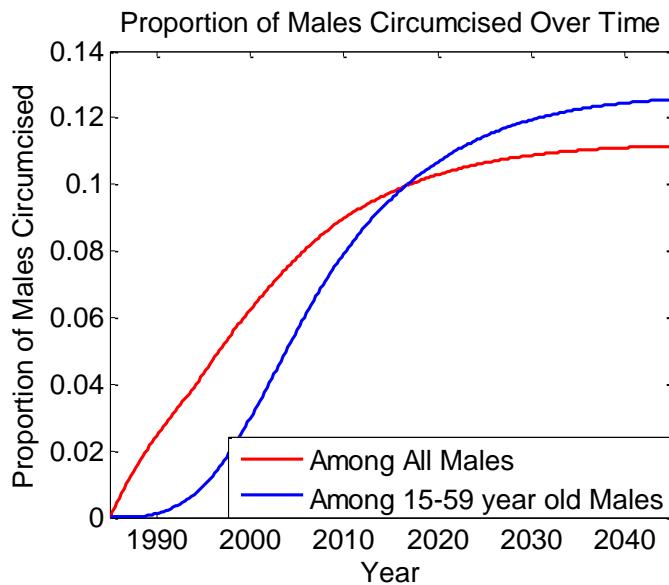


Figure S2. Circumcision prevalence in males. Proportion of males circumcised over time. Note that circumcision among 15 to 59-year-old males surpasses the overall rate because uncircumcised males are less likely to acquire HIV, and thus have lower mortality.

Mortality:

People leave the population due to death or aging past age 79. Mortality is represented by mortality caused by HIV, $\alpha_a^{g,d}$, and all other background mortality, μ_a^g . Mortality caused by HIV varies by stage of disease and age (individuals 0 to 4 years old and 50 to 79 years old are assumed to have elevated risks of death), and individuals on ART are assumed to have no disease-induced mortality (8, 9). The background mortality rate is estimated to be the population mortality rate in 1990, prior to the generalized HIV epidemic.

Disease Transmission:

HIV

Disease transmission is governed by the force of infection, $\lambda_{a,r}^{g,d}(t)$, which determines the number of people who are infected at each time-step.

For HIV:

$$\lambda_{a,r}^{g,d}(t) = \sum_{a'=0}^{15} \sum_{r'=0}^2 \left[c_{g,a,r}^{*a',r'}(t) * \frac{-(\sum_{d'=1}^9 \sum_{v'=1}^5 \ln(1 - \beta^{g,r,v'}) \psi_3 X_{a',r'}^{g',d',v'}(t)) + \ln(1 - \beta^{g,r,6}) \psi_3 \psi_4 X_{a',r'}^{g',9,6}(t))}{\sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{g',d',v'}(t)} \right]$$

The equation variables are:

$c_{g,a,r}^{*a',r'}(t)$	The adjusted number of partners from age a' and sexual risk group r' that an individual has per year
$\beta^{g,r,v'}$	The probability of HIV transmission per partnership between an HIV-positive person of stage v' and HIV-negative person of risk group r

The overall force of infection for a specific age-group and risk-group is the cumulative risk of acquiring HIV from all possible partners.

HPV

Disease transmission is governed by the force of infection, $\lambda_{HPV,a,r}^{g,d,h}$, which determines the number of people that are infected at each time-step.

$$\lambda_{HPV,a,r}^{g,d,h}(t) = \sum_{a'=0}^{15} \sum_{r'=0}^2 \left[c_{g,a,r}^{*a',r'}(t) * \frac{-(\sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=1}^5 \ln(1 - \beta_h^{g,r}) X_{a',r'}^{g',d',v',h,s'}(t))}{\sum_{v'=0}^6 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{h'=0}^1 X_{a',r'}^{g',d',v',h,s'}(t)} \right]$$

The equation variables are:

$c_{g,a,r}^{*a',r'}(t)$	The adjusted number of partners from age a' and sexual risk group r' that an individual has per year
$\beta_h^{g,r}$	The probability of HPV transmission per partnership between an HPV-positive person with HPV-type h and an HPV-negative person of risk group r

Mixing Matrix:

Using methods similar to other models, the mixing matrix, $\rho_{g,a,r}^{a',r'}(t)$, describes patterns of sexual contact by calculating the proportion of one's sexual partners that come from a specific age and sexual-risk group (10).

$$\rho_{g,a,r}^{a',r'}(t) = \left[\epsilon_a \frac{\sum_{r'=0}^2 (c_{a',r'}^{g'} \sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{g',d',v',h',s'}(t))}{\sum_{a'=0}^{15} \sum_{r'=0}^2 (c_{a',r'}^{g'} \sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{g',d',v',h',s'}(t))} + (1 - \epsilon_a) \delta_a^{a'} \right] * \left[\epsilon_r \frac{(c_{a',r'}^{g'} \sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{g',d',v',h',s'}(t))}{\sum_{r'=0}^2 (c_{a',r'}^{g'} \sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{g',d',v',h',s'}(t))} + (1 - \epsilon_r) \delta_r^{r'} \right]$$

where $\delta_r^{r'} = \begin{cases} 1.0 & \text{If } r = r' \\ 0.0 & \text{If } r \neq r' \end{cases}$

$$\begin{aligned} \delta_a^{a'} &= 0.0 && \text{Otherwise} \\ &= 1.0 && \text{If } a = a' = 4 \text{ (for males and females)} \\ &= 0.0 && \text{If } a = 3, a' = 4 \text{ (for females)} \\ &= 0.0 && \text{If } a = 4, a' = 5 \text{ (for females)} \\ &= 1.0 && \text{If } a = 3, a' = 3 \text{ (for females)} \\ &= 0.0 && \text{If } a = 4, a' = 3 \text{ (for males)} \\ &= 0.0 && \text{If } a = 3, a' = 2 \text{ (for males)} \\ &= 1.0 && \text{If } a = 3, a' = 3 \text{ (for males)} \\ &= 0.3 && \text{If } a = a' \\ &= 0.7 && \text{If } a = a' + 1 \text{ (for males)} \\ &&& \text{If } a = a' - 1 \text{ (for females)} \\ &= 0.0 && \text{Otherwise} \end{aligned}$$

Mixing patterns vary between random and assortative, as determined by the parameter ϵ .

Random mixing ($\epsilon = 1$) is mixing proportional to the relative sizes of all compartments and this method is consistent for both random mixing by risk and by age. However, assortative mixing ($\epsilon = 0$) is among groups with similar characteristics and differs for mixing by risk and age. Assortative mixing by risk ($\epsilon_r = 0$) is defined by the identity matrix $\delta_r^{r'}$, whereas assortative mixing by age ($\epsilon_a = 0$) is defined by an off-diagonal matrix $\delta_a^{a'}$. The off-diagonal pattern results in females of age a being more likely to form partnerships with males of age $a = a' - 1$, which is consistent with reports of such age discrepancies in

KZN (11, 12). Although this off-diagonal method results in some age groups having fewer than 100% of their partnerships, those age-groups are $a = 0$ and $a = 15$, which contribute marginally to overall HIV transmission. From 1975 to 1985, assortativity is decreased to reproduce observed HIV prevalence trends at the onset of the epidemic. From 1988 to 2003, ϵ_a and ϵ_r shift to reflect increasing assortativity over the course of the simulation and to reproduce HIV prevalence trends in more recent years. This behavioral change may be explained by the consistent government campaigns against risky sexual behavior (13).

Per-Partnership Probability of Transmission:

The per-partnership probability of transmission, $\beta^{g,r,d'}$, depends on the sexual risk group of the HIV-negative partner and the disease state of the HIV-positive partner. The probabilities of transmission per partnership are:

$$\begin{aligned}\beta^{0,r,v'} &= 1 - (1 - \chi^{v'})^{A_r^0} && \text{For male HIV-negative partners} \\ \beta^{1,r,v'} &= (1 - (1 - \chi^{v'})^{A_r^1}) && \text{For female HIV-negative partners}\end{aligned}$$

$\chi^{g,d'}$ is the per-act probability of transmission for an HIV-positive partner of HIV stage d' , and the exponent, A_r^g , is the number of coital acts based on the HIV-negative partner's sexual risk group and gender.

The per partnership probability of transmission is calculated in a similar manner for HPV. χ^h is the per-act probability of transmission for an HPV-positive partner with HPV type h :

$$\beta_h^{g,r} = 1 - (1 - \chi^h)^{A_r^0}$$

$$\beta_h^{g,r} = (1 - (1 - \chi^h)^{A_r^1})$$

Rate of Partner Change:

Data on sexual behavior and specifically, sexual contact rates, $c_{a,r}^g$, are often subject to biases leading to contact rate data that, when assuming solely heterosexual contact, are inconsistent between

males and females (14). We account for this variability by using an adjusted contact rate, $c_{g,a,r}^{*a',r'}(t)$, which equilibrates the reported number of sexual partners by males and females (10). The adjusted contact rate can be male- or female-driven, as determined by the parameter θ , where $\theta = 1$ when male-driven, $\theta = 0$ when female-driven, and $\theta = 0.5$ when driven equally by contact rates reported by males and females. We assume $\theta = 0.5$ given the lack of data to assume otherwise. The adjusted contact rate for females is:

$$c_{1,a,r}^{*a',r'}(t) = c_{a,r}^1 \rho_{1,a,r}^{a',r'}(t) B_{a,r}^{a',r'}(t)^\theta \left(\frac{\sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{0,d',v',h',s'}(t)}{\sum_{h=0}^3 \sum_{s=0}^8 \sum_{d=0}^9 \sum_{v=0}^6 X_{a,r}^{1,d,v,h,s}(t)} \right)^{-(1-\theta)}$$

For males, the adjusted contact rate is:

$$c_{0,a',r'}^{*a,r}(t) = c_{a,r}^0 \rho_{0,a,r}^{a',r'}(t) B_{a,r}^{a',r'}(t)^{-(1-\theta)} \left(\frac{\sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{0,d',v',h',s'}(t)}{\sum_{h=0}^3 \sum_{s=0}^8 \sum_{d=0}^9 \sum_{v=0}^6 X_{a,r}^{1,d,v,h,s}(t)} \right)^\theta$$

The discrepancy between the two populations, $B_{a,r}^{a',r'}(t)$, is defined as:

$$B_{a,r}^{a',r'}(t) = \frac{c_{a,r}^0 \rho_{0,a,r}^{a',r'}(t) * \sum_{h'=0}^3 \sum_{s'=0}^8 \sum_{d'=0}^9 \sum_{v'=0}^6 X_{a',r'}^{0,d',v',h',s'}(t)}{c_{a,r}^1 \rho_{1,a,r}^{a',r'}(t) * \sum_{h=0}^3 \sum_{s=0}^8 \sum_{d=0}^9 \sum_{v=0}^6 X_{a,r}^{1,d,v,h,s}(t)}$$

Population Aging:

To age the population, one-fifth of each compartment enters the next age group of corresponding gender, sexual risk, and disease state. When individuals age, they also change sexual risk groups; therefore, they redistribute to a fixed sexual-risk profile, $\phi_{a,r}^g$, that varies by age and gender. The model assumes that the probability of an individual entering a given risk group as s/he ages is independent of the individual's current age and risk group. All compartments, except for the youngest and oldest age-groups, experience inflows from the prior age group and outflows into the next age group. The 0 to 4 age-group only receives inflows through births while members transitioning out of the 75 to 79 age-group exit the population. The differential equations that describe the model's aging process are as follows:

$$\frac{dX_{0,r}^{g,d}(t)}{dt} = -\frac{1}{5}X_{0,r}^{g,d}(t) \quad \text{For } a = 0$$

$$\frac{dX_{a,r}^{g,d}(t)}{dt} = -\frac{1}{5}X_{a,r}^{g,d}(t) + \frac{1}{5}\sum_{r=0}^2 X_{a-1,r}^{g,d}(t)\phi_{a-1,r}^g \quad \text{For } a \neq 0$$

Model Calibration:

The model was calibrated to fit HIV prevalence data from KwaZulu-Natal (2003 to 2009). The parameters for HIV transmission probability, sexual partnership duration, and sexual mixing were varied individually and final values were chosen by a combination of visual fit and maximum likelihood estimation. HIV transmission probability was varied from 0.00053 to 0.00097 (15), and the degree of sexual mixing was varied from 0.1 to 1 (10). Parameters for assortativity by age and risk group were calibrated by visual fit. The number of sex acts per year by age group was calibrated using maximum likelihood estimation. Condom usage provided protection against infection 80% of the time (16). Coverage was scaled up linearly from 0% to 25% (50% of individuals using condoms 50% of the time) from 1988 to 2000 to match observed HIV prevalence trends.

In the HPV portion of the model, the following parameters were calibrated using maximum likelihood estimation: age-specific rates of progression of CIN2 to CIN3, CIN3 regression to CIN2, progression of CIN3 to cervical cancer for all HPV types, multiplier for HPV clearance to natural immunity state for HIV-positive women, CIN2 to CIN3 progression multipliers for HIV-positive women, CIN1 to CIN2 progression multipliers for HIV-positive women, HPV acquisition multiplier for women on ART, and per partner transmission probability of HPV 16/18, other 9-valent oncogenic HPV types, and non-vaccine oncogenic HPV types. The age-specific rates of progression of CIN2 to CIN3, CIN3 regression to CIN2, progression CIN3 to cervical cancer for all HPV types, were calibrated by adjusting multiplier values that would be applied across all ages for each parameter, e.g. HPV16/18 associated CIN2 to CIN3 progression rates would be adjusted by the same multiplier value for all ages. These parameters were fitted to point estimates from the literature for CIN2/CIN3 prevalence by HIV status and age in 2014, and female HPV

prevalence by HIV status and age in 2014. Point estimates for model parameters were varied from 0.5x to 1.5x of their originally reported values during the calibration process. The resultant cervical cancer incidence produced by the model was then validated against Globocan data for cervical cancer incidence in 2008 and 2014.

Since a deterministic model was employed, the most probable point estimates for parameters as derived from the maximum likelihood calibration procedure have been reported.

Maximum Likelihood Estimation Procedure

It is assumed that the outcomes of interest, e.g. proportion of women with a CIN3 lesion, are binomially distributed.

The likelihood equation thus takes the following form:

$$L(\vec{\theta}|\vec{x}) = \prod_{i=1}^s \frac{N_i!}{x_i!(N_i-x_i)!} p_i^{x_i} (1-p_i)^{N_i-x_i}$$

Where

$L(\vec{\theta} \vec{x})$	The likelihood of the set of parameters $\vec{\theta}$, given the observed data \vec{x}
$\vec{\theta}$	The set of parameters to be calibrated
\vec{x}	The set of observed occurrences of events
x_i	The number of occurrences of event 1 out of 2 possible events in reported outcome i
N_i	The number of observations in reported outcome i
p_i	The model generated probability of event i
s	The number of reported outcomes

Since $L(\vec{\theta}|\vec{x})$ and $\log(L(\vec{\theta}|\vec{x}))$ are monotonically related, $\log(L(\vec{\theta}|\vec{x}))$ is maximized by searching for $\vec{\theta}$ such that the following is satisfied:

$$\nabla \log(L(\vec{\theta}|\vec{x})) = 0$$

$$\text{Where } \log(L(\vec{\theta}|\vec{x})) = \sum_{i=1}^s (N_i - x_i) \log(1 - p_i) + x_i \log(p_i)$$

Note that the constant term has been omitted as it has no impact on the parameter values obtained by the calibration procedure.

The *patternsearch* function in *MATLAB* R2017b was used to find p_i that minimizes the negative log-likelihood function, which is equivalent to maximizing the log-likelihood function. The following options were used with *patternsearch*:

```
options = psoptimset('UseParallel', true, 'Cache', 'on',...
    'CacheTol', 0.1, 'CompletePoll', 'on', 'TolMesh', 0.1, ...
    'Display','iter','PlotFcn',@psplotbestf);
```

Data used for MLE

i	Criteria	Source	Group	Year	x_i	N_i
1	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	17–19 years	2014	6	48
2	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	20–24 years	2014	12	221
3	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	25–29 years	2014	31	243
4	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	30–34 years	2014	27	175
5	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	35–39 years	2014	33	407
6	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	40–44 years	2014	8	147
7	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	45–49 years	2014	6	76
8	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	50–54 years	2014	2	28
9	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	55–59 years	2014	1	13
10	CIN2/CIN3 Prevalence (HIV+)	McDonald 2014	60–65 years	2014	1	13
11	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	17–19 years	2014	3	191
12	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	20–24 years	2014	19	693
13	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	25–29 years	2014	14	662
14	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	30–34 years	2014	24	666
15	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	35–39 years	2014	65	2,272
16	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	40–44 years	2014	44	1,400
17	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	45–49 years	2014	30	982

18	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	50–54 years	2014	13	617
19	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	55–59 years	2014	4	283.5
20	CIN2/CIN3 Prevalence (HIV-)	McDonald 2014	60–65 years	2014	4	283.5
21	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	17–19 years	2008	39	239
22	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	20–24 years	2008	190	914
23	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	25–29 years	2008	198	905
24	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	30–34 years	2008	124	841
25	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	35–39 years	2008	309	2,679
26	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	40–44 years	2008	95	1,547
27	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	45–49 years	2008	40	1,058
28	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	50–54 years	2008	13	645
29	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	55–59 years	2008	8	296.5
30	HPV Prevalence in HIV+ Women (no CIN2/3)	Allan 2008	60–65 years	2008	8	296.5
31	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	17–19 years	2008	112	191
32	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	20–24 years	2008	242	693
33	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	25–29 years	2008	144	662
34	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	30–34 years	2008	111	666
35	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	35–39 years	2008	374	2,272
36	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	40–44 years	2008	203	1,400
37	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	45–49 years	2008	100	982
38	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	50–54 years	2008	89	617
39	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	55–59 years	2008	37.5	283.5
40	HPV Prevalence in HIV- Women (no CIN2/3)	Allan 2008	60–65 years	2008	37.5	283.5
41	HPV Prevalence in HIV+ Women (all)	McDonald	17-19	2014	36	48

42	HPV Prevalence in HIV+ Women (all)	McDonald	20-24	2014	134	221
43	HPV Prevalence in HIV+ Women (all)	McDonald	25-29	2014	145	243
44	HPV Prevalence in HIV+ Women (all)	McDonald	30-34	2014	96	175
45	HPV Prevalence in HIV+ Women (all)	McDonald	35-39	2014	189	407
46	HPV Prevalence in HIV+ Women (all)	McDonald	40-44	2014	62	147
47	HPV Prevalence in HIV+ Women (all)	McDonald	45-49	2014	33	76
48	HPV Prevalence in HIV+ Women (all)	McDonald	50-54	2014	15	28
49	HPV Prevalence in HIV+ Women (all)	McDonald	55-65	2014	9	26
50	HPV Prevalence in HIV- Women (all)	McDonald	17-19	2014	115	191
51	HPV Prevalence in HIV- Women (all)	McDonald	20-24	2014	261	693
52	HPV Prevalence in HIV- Women (all)	McDonald	25-29	2014	158	662
53	HPV Prevalence in HIV- Women (all)	McDonald	30-34	2014	135	666
54	HPV Prevalence in HIV- Women (all)	McDonald	35-39	2014	439	2272
55	HPV Prevalence in HIV- Women (all)	McDonald	40-44	2014	247	1400
56	HPV Prevalence in HIV- Women (all)	McDonald	45-49	2014	130	982
57	HPV Prevalence in HIV- Women (all)	McDonald	50-54	2014	102	617
58	HPV Prevalence in HIV- Women (all)	McDonald	55-65	2014	83	567
59	HIV Prevalence in Men 2003	Africa Center	15-19	2003	57	5624
60	HIV Prevalence in Men 2003	Africa Center	20-24	2003	455	5141
61	HIV Prevalence in Men 2003	Africa Center	25-29	2003	1027	3643
62	HIV Prevalence in Men 2003	Africa Center	30-34	2003	1253	2773
63	HIV Prevalence in Men 2003	Africa Center	35-39	2003	728	1,956
64	HIV Prevalence in Men 2003	Africa Center	40-44	2003	441	1,638
65	HIV Prevalence in Men 2003	Africa Center	45-49	2003	309	1,362
66	HIV Prevalence in Men 2005	Africa Center	15-19	2005	74	5624
67	HIV Prevalence in Men 2005	Africa Center	20-24	2005	519	5141
68	HIV Prevalence in Men 2005	Africa Center	25-29	2005	1214	3643
69	HIV Prevalence in Men 2005	Africa Center	30-34	2005	1243	2773
70	HIV Prevalence in Men 2005	Africa Center	35-39	2005	707	1956
71	HIV Prevalence in Men 2005	Africa Center	40-44	2005	527	1638
72	HIV Prevalence in Men 2005	Africa Center	45-49	2005	284	1362
73	HIV Prevalence in Men 2006	Africa Center	15-19	2006	41	5624
74	HIV Prevalence in Men 2006	Africa Center	20-24	2006	466	5141
75	HIV Prevalence in Men 2006	Africa Center	25-29	2006	1139	3643
76	HIV Prevalence in Men 2006	Africa Center	30-34	2006	1175	2773
77	HIV Prevalence in Men 2006	Africa Center	35-39	2006	815	1956
78	HIV Prevalence in Men 2006	Africa Center	40-44	2006	533	1638
79	HIV Prevalence in Men 2006	Africa Center	45-49	2006	394	1362
80	HIV Prevalence in Men 2007	Africa Center	15-19	2007	58	5624
81	HIV Prevalence in Men 2007	Africa Center	20-24	2007	552	5141
82	HIV Prevalence in Men 2007	Africa Center	25-29	2007	1106	3643
83	HIV Prevalence in Men 2007	Africa Center	30-34	2007	1116	2773
84	HIV Prevalence in Men 2007	Africa Center	35-39	2007	785	1956

85	HIV Prevalence in Men 2007	Africa Center	40-44	2007	648	1638
86	HIV Prevalence in Men 2007	Africa Center	45-49	2007	393	1362
87	HIV Prevalence in Men 2008	Africa Center	15-19	2008	58	5624
88	HIV Prevalence in Men 2008	Africa Center	20-24	2008	557	5141
89	HIV Prevalence in Men 2008	Africa Center	25-29	2008	1124	3643
90	HIV Prevalence in Men 2008	Africa Center	30-34	2008	1079	2773
91	HIV Prevalence in Men 2008	Africa Center	35-39	2008	911	1956
92	HIV Prevalence in Men 2008	Africa Center	40-44	2008	500	1638
93	HIV Prevalence in Men 2008	Africa Center	45-49	2008	370	1362
94	HIV Prevalence in Men 2009	Africa Center	15-19	2009	52	5624
95	HIV Prevalence in Men 2009	Africa Center	20-24	2009	403	5141
96	HIV Prevalence in Men 2009	Africa Center	25-29	2009	1010	3643
97	HIV Prevalence in Men 2009	Africa Center	30-34	2009	1271	2773
98	HIV Prevalence in Men 2009	Africa Center	35-39	2009	1081	1956
99	HIV Prevalence in Men 2009	Africa Center	40-44	2009	574	1638
100	HIV Prevalence in Men 2009	Africa Center	45-49	2009	498	1362
101	HIV Prevalence in Women 2003	Africa Center	15-19	2003	555	5622
102	HIV Prevalence in Women 2003	Africa Center	20-24	2003	1797	5489
103	HIV Prevalence in Women 2003	Africa Center	25-29	2003	1957	3869
104	HIV Prevalence in Women 2003	Africa Center	30-34	2003	1502	3174
105	HIV Prevalence in Women 2003	Africa Center	35-39	2003	844	2404
106	HIV Prevalence in Women 2003	Africa Center	40-44	2003	540	2075
107	HIV Prevalence in Women 2003	Africa Center	45-49	2003	387	1829
108	HIV Prevalence in Women 2005	Africa Center	15-19	2005	431	5622
109	HIV Prevalence in Women 2005	Africa Center	20-24	2005	1794	5489
110	HIV Prevalence in Women 2005	Africa Center	25-29	2005	1942	3869
111	HIV Prevalence in Women 2005	Africa Center	30-34	2005	1428	3174
112	HIV Prevalence in Women 2005	Africa Center	35-39	2005	909	2404
113	HIV Prevalence in Women 2005	Africa Center	40-44	2005	522	2075
114	HIV Prevalence in Women 2005	Africa Center	45-49	2005	370	1829
115	HIV Prevalence in Women 2006	Africa Center	15-19	2006	489	5622
116	HIV Prevalence in Women 2006	Africa Center	20-24	2006	1732	5489
117	HIV Prevalence in Women 2006	Africa Center	25-29	2006	1804	3869
118	HIV Prevalence in Women 2006	Africa Center	30-34	2006	1505	3174
119	HIV Prevalence in Women 2006	Africa Center	35-39	2006	875	2404
120	HIV Prevalence in Women 2006	Africa Center	40-44	2006	530	2075
121	HIV Prevalence in Women 2006	Africa Center	45-49	2006	320	1829
122	HIV Prevalence in Women 2007	Africa Center	15-19	2007	527	5622
123	HIV Prevalence in Women 2007	Africa Center	20-24	2007	1793	5489
124	HIV Prevalence in Women 2007	Africa Center	25-29	2007	2022	3869
125	HIV Prevalence in Women 2007	Africa Center	30-34	2007	1527	3174
126	HIV Prevalence in Women 2007	Africa Center	35-39	2007	898	2404
127	HIV Prevalence in Women 2007	Africa Center	40-44	2007	698	2075

128	HIV Prevalence in Women 2007	Africa Center	45-49	2007	361	1829
129	HIV Prevalence in Women 2008	Africa Center	15-19	2008	531	5622
130	HIV Prevalence in Women 2008	Africa Center	20-24	2008	1697	5489
131	HIV Prevalence in Women 2008	Africa Center	25-29	2008	1993	3869
132	HIV Prevalence in Women 2008	Africa Center	30-34	2008	1587	3174
133	HIV Prevalence in Women 2008	Africa Center	35-39	2008	968	2404
134	HIV Prevalence in Women 2008	Africa Center	40-44	2008	701	2075
135	HIV Prevalence in Women 2008	Africa Center	45-49	2008	491	1829
136	HIV Prevalence in Women 2009	Africa Center	15-19	2009	621	5622
137	HIV Prevalence in Women 2009	Africa Center	20-24	2009	1794	5489
138	HIV Prevalence in Women 2009	Africa Center	25-29	2009	1896	3869
139	HIV Prevalence in Women 2009	Africa Center	30-34	2009	1692	3174
140	HIV Prevalence in Women 2009	Africa Center	35-39	2009	1071	2404
141	HIV Prevalence in Women 2009	Africa Center	40-44	2009	778	2075
142	HIV Prevalence in Women 2009	Africa Center	45-49	2009	495	1829

Additional Notes on Calibration

Due to the multitude of parameters that were calibrated, it was infeasible to perform an exhaustive search of the parameter space during the calibration process. MATLAB's *patternsearch* optimization tool was used to search regions of the parameter space in an efficient manner. The MLE calibration procedure was performed in two rounds. After the first round of MLE calibration, the model's HPV prevalence output did not match the observed data well. As such, the initial values for HIV-status dependent clearance rates of non-16/18 oncogenic HPV covered by the 9-valent vaccine and non-vaccine oncogenic HPV were reduced by a factor of 0.65. These new values were used as an input to *patternsearch* for the second round of calibration, in addition to the other calibrated values from the first round of MLE calibration. The calibration procedure was stopped when it appeared that the value of the negative log-likelihood function had reached an asymptotic minimum.

Given the vast quantity of parameters in the model, it is highly likely that the model parameters derived through our MLE procedure may only represent one of many possible local optima. Furthermore, there is a strong possibility that these parameters do not represent a global optimum. Due to the non-linear and dynamic nature of this model, slight differences in certain parameter values may

have a material impact on the projected results. Most notably, variations in parameters that are challenging to observe – assortativity by age and risk, partners per year, condom usage, and coital frequency – significantly impact the modeled epidemic trajectory. While model output using these parameters has been validated against observed data where available, model predictions may nevertheless vary substantially from actual outcomes for the aforementioned reasons.

II. Interventions

ART Treatment Enrollment:

Coverage of ART treatment for HIV-positive persons increases from 0% in 2004 to 35% for persons with CD4 ≤200 cells/µL in 2006 as previously observed in KZN (17), then to 45% coverage for male HIV-positive persons in 2014 and 65% coverage for female HIV-positive persons. ART coverage is modeled to reach the expected ART coverages in 2000, 2006, and 2014, and to reach a steady-state by 2025. The steady-state ART coverage depends on the scenario being simulated. ART treatment is assumed to reduce the likelihood of HIV transmission by 96% as suggested by recent studies ($\psi_2 = 0.96$), and persons on ART are expected to have the same life expectancy as HIV-negative persons of similar age and gender, and thus, are assumed not to be subject to HIV-associated mortality (9, 18-21).

Circumcision:

This model includes a background level of circumcision of 10% as currently observed in KZN (3). Several studies show that circumcised males have a 60% ($\psi_0 = 0.6$) lower risk of acquiring HIV. Since circumcision does not reduce the risk of a HIV-positive person transmitting HIV, the model does not track the circumcision status of HIV-positive persons (22-24). The differential equation for HIV-negative circumcised males is:

$$\frac{dX_{a,r}^{0,6,0}(t)}{dt} = b_{r,1}^{0,0}(t) + \sigma_{a,r}^{0,0}X_{a,r}^{1,7,0}(t) - (\mu_a^0 + (1 - \psi_0)\lambda_{a,r}^{0,0}(t) - \pi_{a,r}^{0,6,0}(t))X_{a,r}^{0,6,0}(t)$$

Other models have studied the impact of circumcision in-depth to include wound healing periods and sexual activity (25, 26). However, this model assumes that circumcision is instantaneous.

HPV vaccination:

HPV vaccination begins in 2018 and continues until the end of the simulation in 2100. The HPV vaccine was assumed to confer protection against 90% of oncogenic HPV types and possess a maximum of 80% efficacy (V_{max}) against vaccine-type HPV infections. Vaccine coverage levels of 90%, 70%, and 50% among females aging from the 5-9 age category into the 10-14 age category were modelled. For each of these coverage levels, the effects of waning vaccine immunity were studied by comparing lifelong vaccine efficacy with average vaccine efficacy periods (t_{eff}) of 20, 15, and 10 years after vaccinating at age a_{vax} . Following this period, the efficacy of the vaccine was assumed to wane at a linear rate such that no vaccine efficacy was retained 20 years following the end of the vaccine efficacy period. The model uses the age group of vaccinated compartments as a proxy for the time elapsed since vaccination.

$$\phi_V(a) = V_{max} - \left(\frac{V_{max}}{20} * (a - (t_{eff} + a_{vax})) * u(a - (t_{eff} + a_{vax})) * u(20 - (a - (t_{eff} + a_{vax}))) \right)$$

III. Epidemiological Parameters

Table S1. Initial population size. Age distribution is based on SA 1985 census and scaled to fit KZN's population growth and size profile.

Age Cohort	Initial Population Size		Reference
	Male	Female	
0 – 4	418,189	417,311	US Census,
5 – 9	361,938	361,594	Stats South
10 – 14	327,171	329,333	Africa (27, 28)
15 – 19	289,627	296,947	
20 – 24	262,704	273,204	
25 – 29	235,673	249,396	
30 – 39	197,816	211,839	
35 – 39	160,952	176,470	
40 – 44	132,311	143,351	
45 – 49	110,849	123,441	

50 – 54	89,027	98,355
55 – 59	70,487	82,330
60 – 64	50,094	57,672
65 – 69	35,803	44,482
70 – 74	24,102	33,878
75 – 79	14,240	22,783
TOTAL	2,780,985	2,922,387

Table S2. Sexual risk distribution by age and sex. Values are based on Africa Centre data from KwaZulu Natal, South Africa (29)

Age group	Male risk distribution			Female risk distribution		
	Low-Risk	Moderate-Risk	High-Risk	Low-Risk	Moderate-Risk	High-Risk
0 – 4	1	0	0	1	0	0
5 – 9	1	0	0	1	0	0
10 – 14	0.980	0.015	0.005	0.980	0.015	0.005
15 – 19	0.509	0.408	0.083	0.964	0.034	0.002
20 – 24	0.472	0.443	0.085	0.959	0.039	0.002
25 – 29	0.510	0.411	0.078	0.955	0.042	0.003
30 – 34	0.605	0.342	0.054	0.983	0.016	0.001
35 – 39	0.766	0.203	0.031	0.982	0.017	0.001
40 – 44	0.818	0.168	0.014	0.984	0.016	0.000
45 – 49	0.851	0.148	0.001	0.996	0.003	0.001
50 – 54	0.851	0.148	0.001	0.996	0.003	0.001
55 – 59	0.851	0.148	0.001	0.996	0.003	0.001
60 - 64	0.851	0.148	0.001	0.996	0.003	0.001
65- 69	0.851	0.148	0.001	0.996	0.003	0.001
70 - 74	0.851	0.148	0.001	0.996	0.003	0.001
75 - 79	0.851	0.148	0.001	0.996	0.003	0.001

Table S3. Annual number of sexual partnerships by age, gender, and sexual risk. Values are based on Africa Centre data from KwaZulu Natal, South Africa (29)

Note: No females were found to be in the high risk group for age 30-34. No males or females were found to be in the high risk groups for ages 45-79. As such, members of the high risk groups in these age groups were assumed to contribute minimally to contact patterns and were assigned one partner per year.

Partnerships per year	Males			Females		
	Age group	Low-Risk	Moderate-Risk	High-Risk	Low-Risk	Moderate-Risk
0 – 4		0	0	0	0	0

5 – 9	0	0	0	0	0	0
10 – 14	0.01	0.12	1.20	0.01	0.12	1.20
15 – 19	0.66	2.55	6.96	0.67	2.21	6.50
20 – 24	0.70	2.55	7.67	0.79	2.25	10.00
25 – 29	0.77	2.56	6.97	0.81	2.27	5.33
30 – 34	0.77	2.48	5.84	0.76	2.06	1
35 – 39	0.78	2.41	6.22	0.76	2.27	9.00
40 – 44	0.84	2.42	7.75	0.69	2.27	1
45 – 49	0.72	2.33	1	0.69	2.27	1
50 – 54	0.72	2.33	1	0.69	2.27	1
55 – 59	0.72	2.33	1	0.69	2.27	1
60 - 64	0.72	2.33	1	0.69	2.27	1
65- 69	0.72	2.33	1	0.69	2.27	1
70 - 74	0.72	2.33	1	0.69	2.27	1
75 - 79	0.72	2.33	1	0.69	2.27	1

Table S4. Background mortality. (30) (31)

Background mortality		
Age Group	Male	Female
0 – 4	0.009773697	0.008805723
5 – 9	0.000704792	0.000524573
10 – 14	0.00066512	0.000488779
15 – 19	0.001534298	0.000903528
20 – 24	0.003030028	0.001691595
25 – 29	0.00415259	0.002071948
30 – 34	0.004986294	0.002460107
35 – 39	0.005808116	0.002992553
40 – 44	0.007524643	0.003941347
45 – 49	0.010206454	0.005357599
50 – 54	0.014201689	0.007541082
55 – 59	0.019689808	0.010540155
60 - 64	0.026650488	0.015759592
65- 69	0.036763609	0.022837523
70 - 74	0.051790401	0.033336893
75 - 79	0.083577388	0.061722847

Table S5. Fertility rate by age and HIV status. Females on ART are assumed to have equal fertility to HIV-negative females.

Before 1995

Age Cohort	Fertility Rate (per year)					Reference
	Uninfected	Acute	>350	200-350	<200	
	RR=1	RR=1	RR=0.4	RR=0.42	RR=0.59	
0 – 4	0	0	0	0	0	Anderson <i>et al.</i>
5 – 9	0	0	0	0	0	Ross <i>et al.</i>
10 – 14	0	0	0	0	0	(12, 32)
15 – 19	0.1414	0.1414	0.1414	0.082012	0.082012	
20 – 24	0.278	0.278	0.278	0.16124	0.16124	
25 – 29	0.2836	0.2836	0.2836	0.164488	0.164488	
30 – 34	0.2112	0.2112	0.2112	0.122496	0.122496	
35 – 39	0.1348	0.1348	0.1348	0.078184	0.078184	
40 – 44	0.0542	0.0542	0.0542	0.031436	0.031436	
45 – 49	0.0176	0.0176	0.0176	0.010208	0.010208	
50 – 54	0	0	0	0	0	
55 – 59	0	0	0	0	0	
60 – 64	0	0	0	0	0	
65 – 69	0	0	0	0	0	
70 – 74	0	0	0	0	0	
75 – 79	0	0	0	0	0	

2005 onwards

Age Cohort	Fertility Rate (per year)					Reference
	Uninfected	Acute	>350	200-350	<200	
	RR=1	RR=1	RR=0.42	RR=0.42	RR=0.59	
0 – 4	0	0	0	0	0	Anderson <i>et al.</i>
5 – 9	0	0	0	0	0	Ross <i>et al.</i>
10 – 14	0	0	0	0	0	(12, 32)
15 – 19	0.0707	0.0707	0.0707	0.041006	0.041006	
20 – 24	0.139	0.139	0.139	0.08062	0.08062	
25 – 29	0.1418	0.1418	0.1418	0.082244	0.082244	
30 – 34	0.1056	0.1056	0.1056	0.061248	0.061248	
35 – 39	0.0674	0.0674	0.0674	0.039092	0.039092	
40 – 44	0.0271	0.0271	0.0271	0.015718	0.015718	
45 – 49	0.0088	0.0088	0.0088	0.005104	0.005104	
50 – 54	0	0	0	0	0	
55 – 59	0	0	0	0	0	
60 – 64	0	0	0	0	0	
65 – 69	0	0	0	0	0	
70 – 74	0	0	0	0	0	

75 – 79	0	0	0	0
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Fertility rates are changed linearly from 1995 to 2005 so that the model's population growth resembles actual population growth patterns

Table S6. HIV-associated mortality. Values are estimates are from observational studies of untreated HIV-positive persons. Persons age 0 to 4 and older than 50 are assumed to have greater mortality as observed.

Age Cohort	HIV Mortality				Reference
	Acute	CD4>350	CD4 200-350	CD4<200	
0 – 4	0.47	0.47	0.47	0.47	Newell <i>et al.</i> (33)
5 – 49	0.01	0.05	0.08	0.27	Badri <i>et al.</i> (34)
50 – 59	0.02	0.10	0.16	0.54	Adler <i>et al.</i> (8)
60 - 79	0.02	0.10	0.16	0.54	Adler <i>et al.</i> (8)

Table S7. Probability of HIV transmission by viral load.

Baseline Transmission Probability	Increase in transmission probability by HIV stage					Reference	
	Acute	VL≤1,000	VL 1,000- 10,000	VL 10,000- 50,000	VL>50,000		
0.0006	7	1	5.8	6.9	11.9	0.04	Quinn <i>et al.</i> , Boily <i>et al.</i> (15, 35)

Table S8. The duration of time in each CD4 and viral load stage by sex.

CD4 Transition	Acute	CD4>500	500-350	350-200
Time for Males (years)	0.25	1.71	1.05	4.71
Time for Females (years)	0.25	1.94	1.35	6.71
Viral Load Transition	Acute	VL≤1,000	1,000-10,000	10,000-50,000
Time for Males (years)	0.25	3.44	1.45	3.04
Time for Females (years)	0.25	3.06	2.27	5.45

Table S9. Proportion of births from HIV-positive females that results in mother-to-child transmission.
The rate decreases linearly from 2004 to 2005 and from 2005 to 2008.

Year	MTCT Rate	Reference
Before 2004	0.34	Bobat <i>et al.</i> (5)
2005	0.202	Rollins <i>et al.</i> (7)
After 2008	0.071	Horwood <i>et al.</i> (6)

Table S10. The number of coital acts per partnership by sex, age, and sexual risk group. Values are calibrated to fit age-specific HIV and HPV prevalence data.

Coital acts per partnership			
MALES			
Age group	Risk Group		
	Low	Medium	High
0 - 4	0.0	0.0	0.0
5 - 9	0.0	0.0	0.0
10 - 14	11.7	7.0	3.4
15 - 19	23.4	14.0	6.7
20 - 24	163.8	98.3	47.2
25-29	234.0	140.4	67.4
30 - 34	165.5	99.3	47.7
35 - 39	117.0	70.2	33.7
40 - 44	82.7	49.6	23.8
45 - 49	58.5	35.1	16.8
50 - 54	41.4	24.8	11.9
55 - 59	29.3	17.6	8.4
60 - 64	20.7	12.4	6.0
65- 69	14.6	8.8	4.2
70 - 74	10.3	6.2	3.0
75 - 79	7.3	4.4	2.1
FEMALES			
Age group	Low	Medium	High
	0.0	0.0	0.0
0 - 4	0.0	0.0	0.0
5 - 9	0.0	0.0	0.0
10 - 14	11.7	7.0	4.4
15 - 19	163.8	98.3	61.9
20 - 24	234.0	140.4	88.5
25-29	165.5	99.3	62.5
30 - 34	117.0	70.2	44.2
35 - 39	57.9	34.7	21.9
40 - 44	41.0	24.6	15.5
45 - 49	20.7	12.4	7.8
50 - 54	29.3	17.6	11.1
55 - 59	20.7	12.4	7.8

60 - 64	14.6	8.8	5.5
65- 69	10.3	6.2	3.9
70 - 74	7.3	4.4	2.8
75 - 79	5.2	3.1	2.0

Table S11. Sexual mixing by age and sexual risk group. The mixing parameter varies from random ($\epsilon = 1$) to assortative ($\epsilon = 0$), calibrated to fit age-specific HIV incidence and prevalence data.

Mixing		
Year	ϵ_a (age)	ϵ_r (sexual risk)
1985 and before	0.3	0.3
1988	0.4	0.4
2003 and after	0.3	0.3

Table S12. Age-specific HIV prevalence data (36)

Male

Calibration

	2003	2005	2006	2007	2008	2009
15-19	1.01	1.32	0.73	1.03	1.03	0.92
20-24	8.85	10.10	9.06	10.74	10.83	7.84
25-29	28.19	33.32	31.27	30.36	30.85	27.72
30-34	45.19	44.83	42.37	40.25	38.91	45.83
35-39	37.22	36.15	41.67	40.13	46.57	55.27
40-44	26.92	32.17	32.54	39.56	30.53	35.04
45-49	22.69	20.85	28.93	28.85	27.17	36.56

Validation

	2010	2011	2012	2013	2014	2015	2016
15-19	9.29	9.02	10.45	9.33	10.37	11	9.35
20-24	31.41	31.68	30.64	33.95	34.56	34.12	33.42
25-29	53.27	51.72	50.8	51.33	51.94	53.98	52.41
30-34	59.18	61.35	58.66	64.9	62.57	64.71	63.09
35-39	53.97	54.08	58.77	65.12	65.28	64.66	66.95
40-44	42.69	43.27	45.29	49.16	54.25	56.37	61.28
45-49	32.34	34.3	39.18	41.47	48.21	49.57	50.23

Female***Calibration***

	2003	2005	2006	2007	2008	2009
15-19	9.87	7.67	8.70	9.37	9.45	11.05
20-24	32.74	32.68	31.55	32.67	30.92	32.68
25-29	50.58	50.19	46.63	52.26	51.51	49.00
30-34	47.32	44.99	47.42	48.11	50.00	53.31
35-39	35.11	37.81	36.40	37.35	40.27	44.55
40-44	26.02	25.16	25.54	33.64	33.78	37.49
45-49	21.16	20.23	17.50	19.74	26.85	27.06

Validation

	2010	2011	2012	2013	2014	2015	2016
15-19	1.6	1.85	2.75	3.46	2.87	3.95	4.5
20-24	9.56	8.02	9.87	9.65	11.86	7.19	8.02
25-29	28.99	21.92	24.88	29.84	35.4	27.65	27.31
30-34	46.47	44.51	39.49	47.22	46.35	41.64	42.08
35-39	52.03	44.3	49.61	63.33	51.41	52.05	51.35
40-44	41.73	41.53	51.55	51.64	59.4	52.69	51.18
45-49	36.64	37.12	33.01	40	40.54	44.52	52.17

Table S13. Overall HIV prevalence (Africa Center Data) (36)

Year	Overall
2010	29.04
2011	29.05
2012	29.32
2013	31.19
2014	33.81
2015	33.82
2016	34.45

Table S14. HIV prevalence (%) by sex over time in KwaZulu Natal(29)

Year	Men	Women
2005	20	28.9
2006	20.1	28.8
2007	20.8	31.1
2008	20.3	31.8

2009	21.2	32.6
2010	22.4	35.9
2011	20.8	36.2
2012	23.7	38.3
2013	27.9	41.1

Table S15. ART coverage over time (37)

Year	ART coverage (%)
2002	0
2003	0
2004	1
2005	2
2006	3
2007	6
2008	9
2009	14
2010	19
2011	27
2012	34
2013	40
2014	45
2015	48

Table S16. HPV incidence multipliers

Original

HPV incidence multiplier by type and CD4 count(38)		
	vaccine types	non vaccine types
<200	2.2	2.5
200-350	2.1	2.3
350-500	1.9	2.1
>500	1.7	2.0

Calibrated

HPV incidence multiplier by type and CD4 count, ART status			
	HPV 16/18	Other 9-valent high risk	Non-vaccine high risk
<200	1.006	2.3	2.5
200-350	1.098	2.5	2.8
350-500	1.19	2.7	3.0
>500	1.28	2.9	3.2
ART	2.0065	2.0065	2.0065

Table S17. HPV clearance multipliers

Original

HPV clearance multipliers(38)	
>500	0.70
350-500	0.55
200-350	0.45
>200	0.40

Calibrated values

HPV clearance multipliers(38)	
>500	0.60
350-500	0.55
200-350	0.45
>200	0.30

Table S18. HPV prevalence in men in South Africa (39)

HIV+						HIV-					
	n	N	prop	LB	UB		n	N	prop	LB	UB
18-25	6	8	0.75	0.45	1.00	18-25	15	35	0.43	0.26	0.59
26-35	39	63	0.62	0.50	0.74	26-35	22	93	0.24	0.15	0.32
36-45	33	66	0.50	0.38	0.62	36-45	22	101	0.22	0.14	0.30
46-66	6	21	0.29	0.09	0.48	46-66	16	84	0.19	0.11	0.27
TOTAL	86	158	0.54	0.47	0.62	TOTAL	70	313	0.22	0.18	0.27

Table S19. HPV prevalence in women in South Africa (39)

HIV+						HIV-					
	n	N	prop	LB	UB		n	N	prop	LB	UB
18-25	32	44	0.73	0.60	0.86	18-25	14	41	0.34	0.20	0.49
26-35	52	129	0.40	0.32	0.49	26-35	18	59	0.31	0.19	0.42
36-45	46	71	0.65	0.54	0.76	36-45	10	63	0.16	0.07	0.25
46-66	14	33	0.42	0.26	0.59	46-66	5	44	0.11	0.02	0.21
TOTAL	144	277	0.52	0.46	0.58	TOTAL	47	207	0.23	0.17	0.28

Table S20. Cervical cancer mortality by stage and HIV status(40, 41)*

	Stage 1	Stage 2-3	Stage 4
HIV negative	0.0052	0.0125129	0.043395
HIV + on ART	0.008007	0.0192699	0.066828
HIV + CD4 >500	0.008007	0.0192699	0.066828
HIV + CD4 350-500	0.009723	0.0233992	0.081148
HIV + CD4 250-350	0.011803	0.0284044	0.098506
HIV + CD4 <250	0.014299	0.0344106	0.119336

*Cervical cancer mortality rates in HIV negative women were obtained from Sankaranarayanan et al and multiplied by the relative increase in cervical cancer mortality by CD4 count found in Dryden Peterson et al.

Table S21. HPV prevalence in women without CIN23 (42)

	HIV+					HIV-				
	n	N	prop	LB	UB	n	N	prop	LB	UB
17–19 years	30	48	0.63	0.49	0.76	112	191	0.59	0.52	0.66
20–24 years	122	221	0.55	0.49	0.62	242	693	0.35	0.31	0.38
25–29 years	114	243	0.47	0.41	0.53	144	662	0.22	0.19	0.25
30–34 years	69	175	0.39	0.32	0.47	111	666	0.17	0.14	0.19
35–39 years	156	407	0.38	0.34	0.43	374	2,272	0.16	0.15	0.18
40–44 years	54	147	0.37	0.29	0.45	203	1,400	0.15	0.13	0.16
45–49 years	27	76	0.36	0.25	0.46	100	982	0.10	0.08	0.12
50–54 years	13	28	0.46	0.28	0.65	89	617	0.14	0.12	0.17
55–59 years	4	13	0.31	0.06	0.56	37.5	283.5	0.13	0.09	0.17
60–65 years	3	13	0.23	0.00	0.46	37.5	283.5	0.13	0.09	0.17
All ages	592	1,371	0.43	0.00	0.00	1450	8,050	0.18	0.17	0.19

Table S22. CIN23 prevalence by HIV status (42)

	HIV+					HIV-				
	n	N	prop	LB	UB	n	N	prop	LB	UB
17–19 years	6	48	0.125	0.03	0.22	3	191	0.016	0.00	0.03
20–24 years	12	221	0.054	0.02	0.08	19	693	0.027	0.02	0.04
25–29 years	31	243	0.128	0.09	0.17	14	662	0.021	0.01	0.03
30–34 years	27	175	0.154	0.10	0.21	24	666	0.036	0.02	0.05
35–39 years	33	407	0.081	0.05	0.11	65	2,272	0.029	0.02	0.04
40–44 years	8	147	0.054	0.02	0.09	44	1,400	0.031	0.02	0.04
45–49 years	6	76	0.079	0.02	0.14	30	982	0.031	0.02	0.04
50–54 years	2	28	0.071	0.00	0.17	13	617	0.021	0.01	0.03
55–59 years	1	13	0.077	0.00	0.22	4	283.5	0.014	0.00	0.03
60–65 years	1	13	0.077	0.00	0.22	4	283.5	0.014	0.00	0.03
All ages	127	1,371	0.093	0.08	0.11	220	8,050	0.027	0.02	0.03

Table S23. CIN23 prevalence by HIV status (43)

HIV+	%	HIV-	%
17-19	12.5	17-19	1.4
20-24	5.3	20-24	2.6
25-29	12.7	25-29	1.9
30-34	15.4	30-34	3.3
35-39	8.0	35-39	2.7
40-44	5.3	40-44	2.9
45-49	7.7	45-49	2.9
50-54	7.0	50-54	1.9
55-65	7.6	55-65	1.1

Table S24. CIN1 to CIN2 and CIN2 to CIN3 multiplier (44)

Original

CIN23 multiplier	
>500	1
350-500	1.75
200-350	2.3
<200	2.66

Calibrated

CIN23 multiplier	
>500	1
350-500	1.3
200-350	1.6
<200	2.0

CIN1 to CIN2 Multiplier

Original

CIN12 multiplier	
>500	1
350-500	1.75
200-350	2.3
<200	2.66

Calibrated

CIN12 multiplier	
>500	1.25
350-500	3.5
200-350	4.8
<200	5.16

Natural Immunity Clearance Rate

0.024 (45)

Natural Immunity Multiplier (*Derived through calibration*)

Age Group	16/18
0-4	0.99000
5-9	0.99000
10-14	0.99000
15-19	0.99000
20-24	0.99000
25-29	0.98415
30-34	0.97488
35-39	0.96019
40-44	0.93690
45-49	0.90000
50-54	0.90000
55-59	0.90000
60-64	0.90000
65-69	0.90000
70-74	0.90000
75-79	0.90000

Natural Immunity Clearance Multiplier for HIV-positive/on ART

ART status /CD4 count multipliers
>500/on ART
350-500
200-350
<200

6.8333
7.8664
9.4444
14.1670

Table S25. CIN1 to CIN2, CIN2 to CIN3, and CIN3 to CC transition rates

Adapted from CCNSW transition rates. Transition rates were given by age group (10-25, 25-45, 50-70, 70+). In order to adapt these rates to our model's 5-year age groups (0-4, 5-9, ..., 74-79), a 4 age-group moving average was applied to the original transition rate data.

a) Original

Age Index	HPV_1 6 to Well	HPV_1 6 to HPV_1 6	HPV_1 6 to CIN1_1 6	HPV_1 6 to CIN2_1 6	CIN1_1 6 to CIN3_1 6	CIN1_1 6 to Well_1 6	CIN1_1 6 to HPV_1 6	CIN1_1 6 to CIN2_1 6	CIN1_1 6 to CIN3_1 6	CIN2_1 6 to Well_1 6	CIN2_1 6 to HPV_1 6	CIN2_1 6 to CIN1_1 6	CIN2_1 6 to CIN2_1 6	CIN2_1 6 to CIN3_1 6	CIN3_1 6 to Well_1 6	CIN3_1 6 to HPV_1 6	CIN3_1 6 to CIN1_1 6	CIN3_1 6 to CIN2_1 6	CIN3_1 6 to CIN3_1 6	CIN3_1 6 to Localis ed	
0 - 24	0.591	0.133	0.209	0.067	0.000	0.177	0.022	0.731	0.035	0.035	0.245	0.026	0.092	0.505	0.132	0.000	0.000	0.053	0.037	0.909	0.001
25 - 49	0.436	0.419	0.119	0.020	0.000	0.177	0.022	0.714	0.040	0.041	0.245	0.026	0.092	0.416	0.215	0.000	0.000	0.037	0.032	0.911	0.014
50-69	0.264	0.622	0.093	0.007	0.000	0.177	0.022	0.689	0.053	0.044	0.245	0.026	0.092	0.339	0.284	0.000	0.000	0.015	0.009	0.929	0.032
70-79	0.233	0.638	0.093	0.007	0.000	0.177	0.022	0.674	0.053	0.044	0.245	0.026	0.092	0.282	0.325	0.000	0.000	0.007	0.005	0.920	0.038

Age Index	HPV_1 8 to Well	HPV_1 8 to HPV_1 8	HPV_1 8 to CIN1_1 8	HPV_1 8 to CIN2_1 8	CIN1_1 8 to CIN3_1 8	CIN1_1 8 to Well_1 8	CIN1_1 8 to HPV_1 8	CIN1_1 8 to CIN2_1 8	CIN1_1 8 to CIN3_1 8	CIN2_1 8 to Well_1 8	CIN2_1 8 to HPV_1 8	CIN2_1 8 to CIN1_1 8	CIN2_1 8 to CIN2_1 8	CIN2_1 8 to CIN3_1 8	CIN3_1 8 to Well_1 8	CIN3_1 8 to HPV_1 8	CIN3_1 8 to CIN1_1 8	CIN3_1 8 to CIN2_1 8	CIN3_1 8 to CIN3_1 8	CIN3_1 8 to Localis ed	
0 - 24	0.593	0.132	0.208	0.066	0.000	0.177	0.022	0.731	0.035	0.035	0.246	0.026	0.092	0.504	0.132	0.000	0.000	0.053	0.038	0.908	0.001
25 - 49	0.438	0.418	0.119	0.020	0.000	0.177	0.022	0.714	0.040	0.041	0.246	0.026	0.092	0.416	0.215	0.000	0.000	0.038	0.032	0.911	0.014
50-69	0.265	0.622	0.093	0.007	0.000	0.177	0.022	0.689	0.053	0.044	0.246	0.026	0.092	0.338	0.283	0.000	0.000	0.015	0.009	0.929	0.032
70-79	0.234	0.637	0.093	0.007	0.000	0.177	0.022	0.673	0.053	0.044	0.246	0.026	0.092	0.282	0.324	0.000	0.000	0.007	0.005	0.920	0.038

Age Index	HPV_o hr to Well	HPV_o hr to HPV_o hr	HPV_o hr to CIN1_o hr	HPV_o hr to CIN2_o hr	CIN1_o hr to CIN3_o hr	CIN1_o hr to Well_o hr	CIN1_o hr to HPV_o hr	CIN1_o hr to CIN2_o hr	CIN1_o hr to CIN3_o hr	CIN2_o hr to Well_o hr	CIN2_o hr to HPV_o hr	CIN2_o hr to CIN1_o hr	CIN2_o hr to CIN2_o hr	CIN2_o hr to CIN3_o hr	CIN3_o hr to Well_o hr	CIN3_o hr to HPV_o hr	CIN3_o hr to CIN1_o hr	CIN3_o hr to CIN2_o hr	CIN3_o hr to CIN3_o hr	CIN3_o hr to Localis ed	
0 - 24	0.786	0.047	0.127	0.039	0.000	0.285	0.038	0.636	0.020	0.020	0.384	0.045	0.153	0.339	0.079	0.000	0.000	0.089	0.064	0.847	0.001
25 - 49	0.628	0.284	0.071	0.012	0.000	0.285	0.038	0.624	0.023	0.024	0.384	0.045	0.153	0.281	0.131	0.000	0.000	0.064	0.054	0.869	0.008
50-69	0.410	0.517	0.055	0.004	0.000	0.285	0.038	0.606	0.031	0.026	0.384	0.045	0.153	0.228	0.176	0.000	0.000	0.026	0.016	0.926	0.018
70-79	0.367	0.545	0.055	0.004	0.000	0.285	0.038	0.590	0.031	0.026	0.384	0.045	0.153	0.185	0.204	0.000	0.000	0.013	0.009	0.927	0.022

b) Calibrated Rates

Infected to CIN 1				CIN1 to CIN2				CIN2 to CIN3				CIN3 to CC	
Age Group	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk	
0-4	0.2421	0.1468	0.1761	0.0491	0.0295	0.0393	0.0901	0.0592	0.0237	0.0015	0.0006	0.0007	
5-9	0.2421	0.1468	0.1761	0.0491	0.0295	0.0393	0.1202	0.0789	0.0316	0.0020	0.0008	0.0009	
10-14	0.2421	0.1468	0.1761	0.0491	0.0295	0.0393	0.1202	0.0789	0.0316	0.0020	0.0008	0.0009	
15-19	0.2421	0.1468	0.1761	0.0491	0.0295	0.0393	0.1393	0.0920	0.0368	0.0068	0.0026	0.0031	
20-24	0.2421	0.1468	0.1761	0.0473	0.0286	0.0380	0.1583	0.1051	0.0420	0.0116	0.0044	0.0053	
25-29	0.1291	0.0768	0.0921	0.0455	0.0277	0.0366	0.1774	0.1181	0.0473	0.0164	0.0062	0.0074	
30-34	0.1291	0.0768	0.0921	0.0436	0.0268	0.0352	0.1965	0.1312	0.0525	0.0212	0.0080	0.0096	
35-39	0.1291	0.0768	0.0921	0.0418	0.0259	0.0339	0.1965	0.1312	0.0525	0.0212	0.0080	0.0096	
40-44	0.1291	0.0768	0.0921	0.0400	0.0250	0.0325	0.2123	0.1425	0.0570	0.0280	0.0106	0.0127	
45-49	0.1291	0.0768	0.0921	0.0382	0.0241	0.0311	0.2282	0.1537	0.0615	0.0349	0.0132	0.0159	
50-54	0.0963	0.0570	0.0684	0.0364	0.0232	0.0298	0.2440	0.1650	0.0660	0.0417	0.0158	0.0190	
55-59	0.0963	0.0570	0.0684	0.0345	0.0223	0.0284	0.2599	0.1762	0.0705	0.0486	0.0184	0.0221	
60-64	0.0963	0.0570	0.0684	0.0327	0.0214	0.0270	0.2693	0.1831	0.0732	0.0507	0.0193	0.0231	
65-69	0.0963	0.0570	0.0684	0.0309	0.0205	0.0257	0.2788	0.1900	0.0760	0.0529	0.0201	0.0241	
70-74	0.0963	0.0570	0.0684	0.0309	0.0205	0.0257	0.2978	0.2038	0.0815	0.0572	0.0217	0.0261	
75-79	0.0963	0.0570	0.0684	0.0309	0.0205	0.0257	0.2978	0.2038	0.0815	0.0572	0.0217	0.0261	

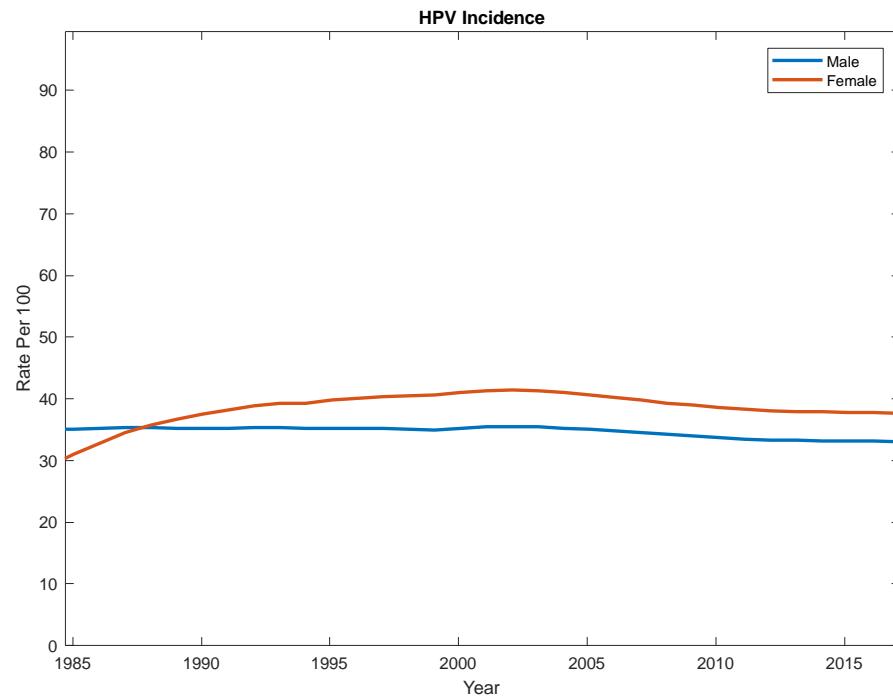
CIN1 to Natural Immunity				CIN2 to CIN1				CIN3 to CIN2				
Age Group	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk	16/18	Non-4v (9v covered)	Other High Risk
0-4	0.1217	0.1615	0.1292	0.2185	0.3456	0.2765	0.0713	0.1207	0.0965	0.1217	0.1615	0.1292
5-9	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0713	0.1207	0.0965	0.1217	0.1615	0.1292
10-14	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0713	0.1207	0.0965	0.1217	0.1615	0.1292
15-19	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0713	0.1207	0.0965	0.1217	0.1615	0.1292
20-24	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0713	0.1207	0.0965	0.1217	0.1615	0.1292
25-29	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0534	0.0906	0.0725	0.1217	0.1615	0.1292
30-34	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0534	0.0906	0.0725	0.1217	0.1615	0.1292

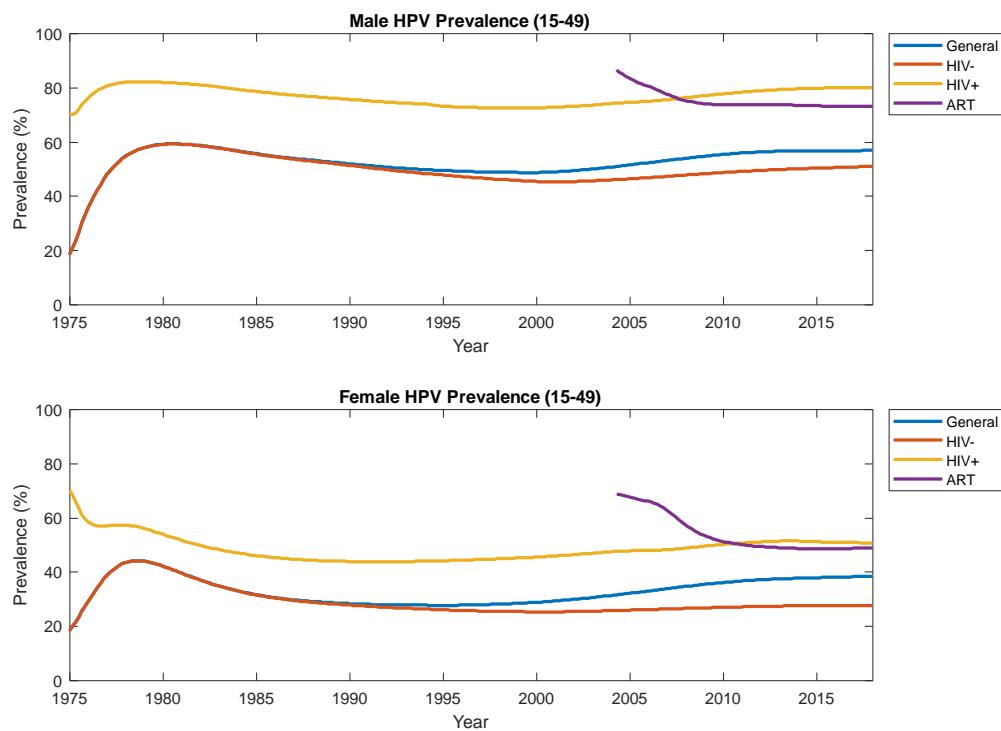
35-39	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0534	0.0906	0.0725
40-44	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0534	0.0906	0.0725
45-49	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0534	0.0906	0.0725
50-54	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0196	0.0335	0.0268
55-59	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0196	0.0335	0.0268
60-64	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0196	0.0335	0.0268
65-69	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0196	0.0335	0.0268
70-74	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0099	0.0171	0.0137
75-79	0.1217	0.1615	0.1292	0.2914	0.4608	0.3687	0.0099	0.0171	0.0137

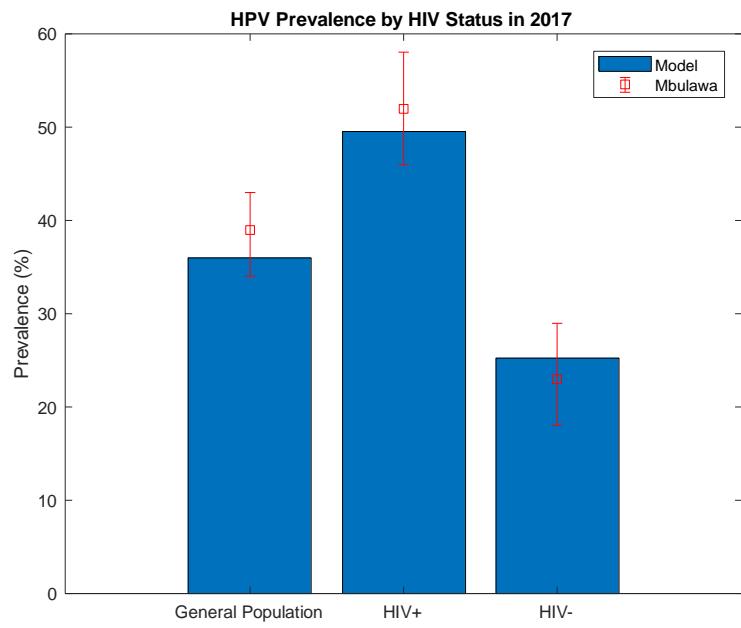
Table S26. CC transition rates

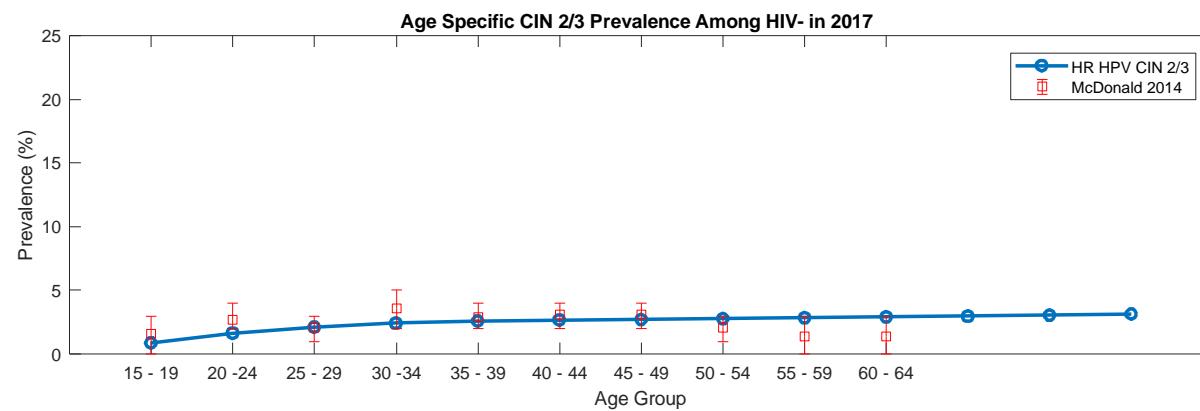
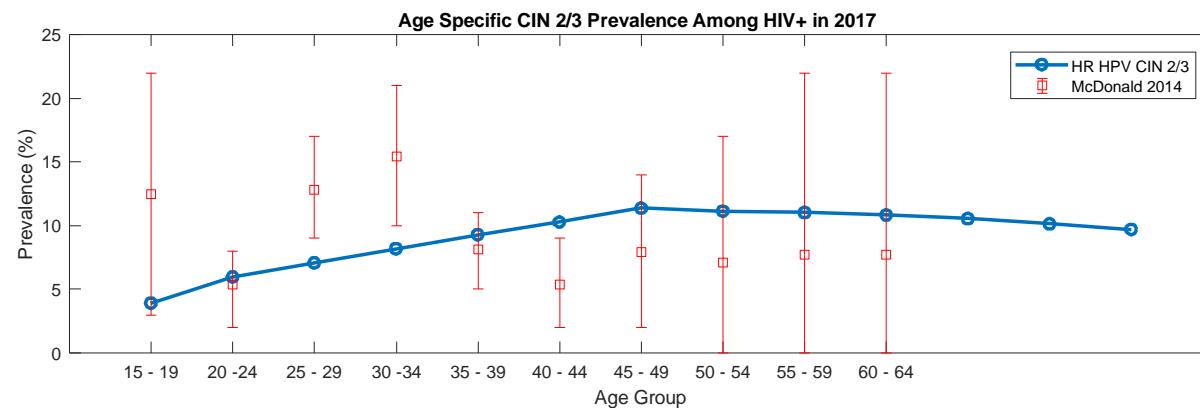
Stage I -> Stage II/III	0.02
Stage II/III -> Stage IV	0.025

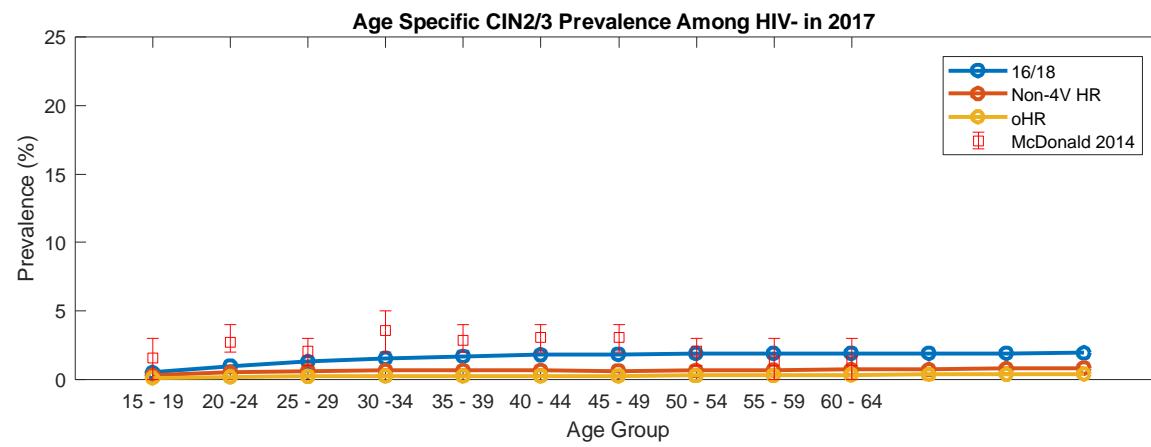
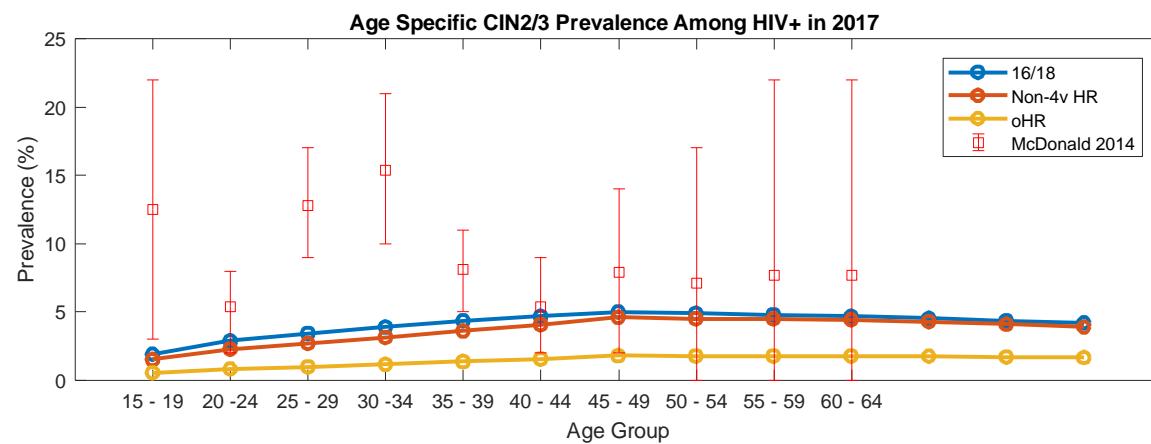
IV. Calibration Outputs

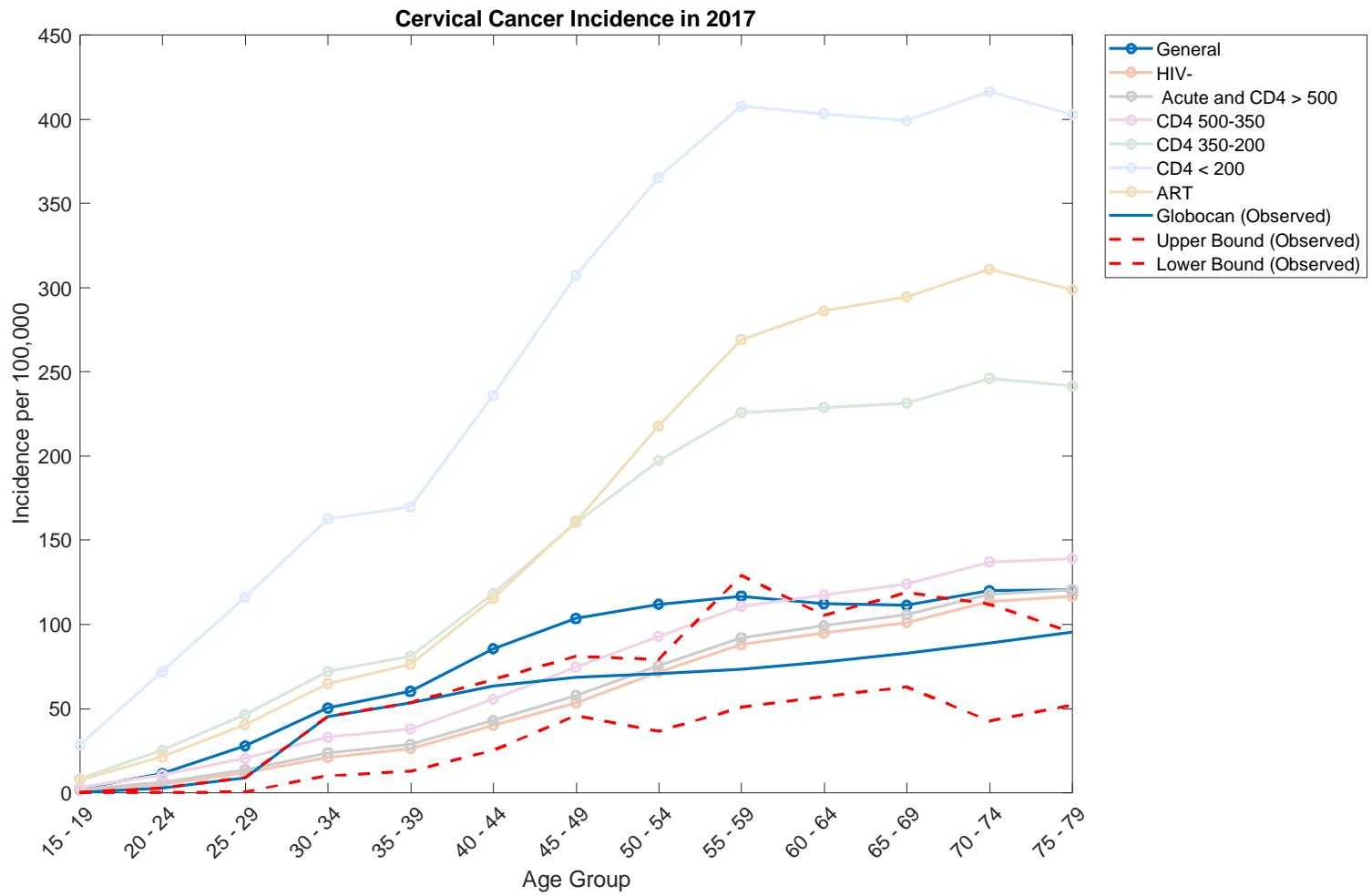


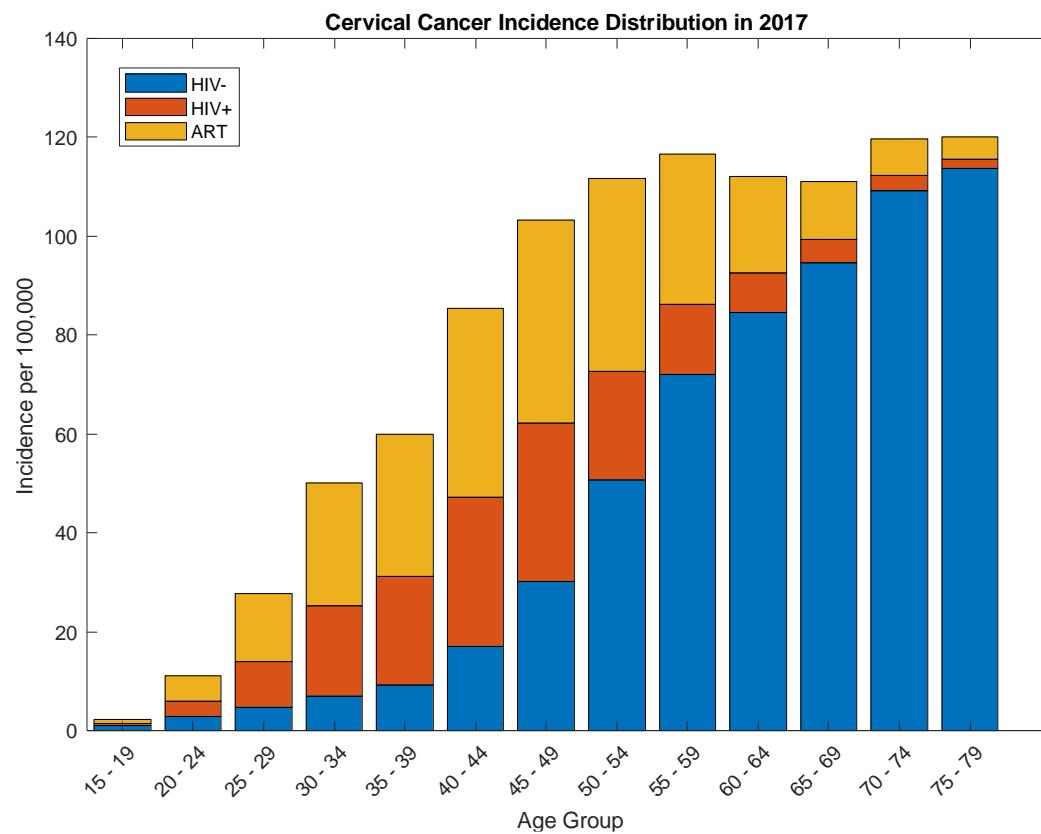


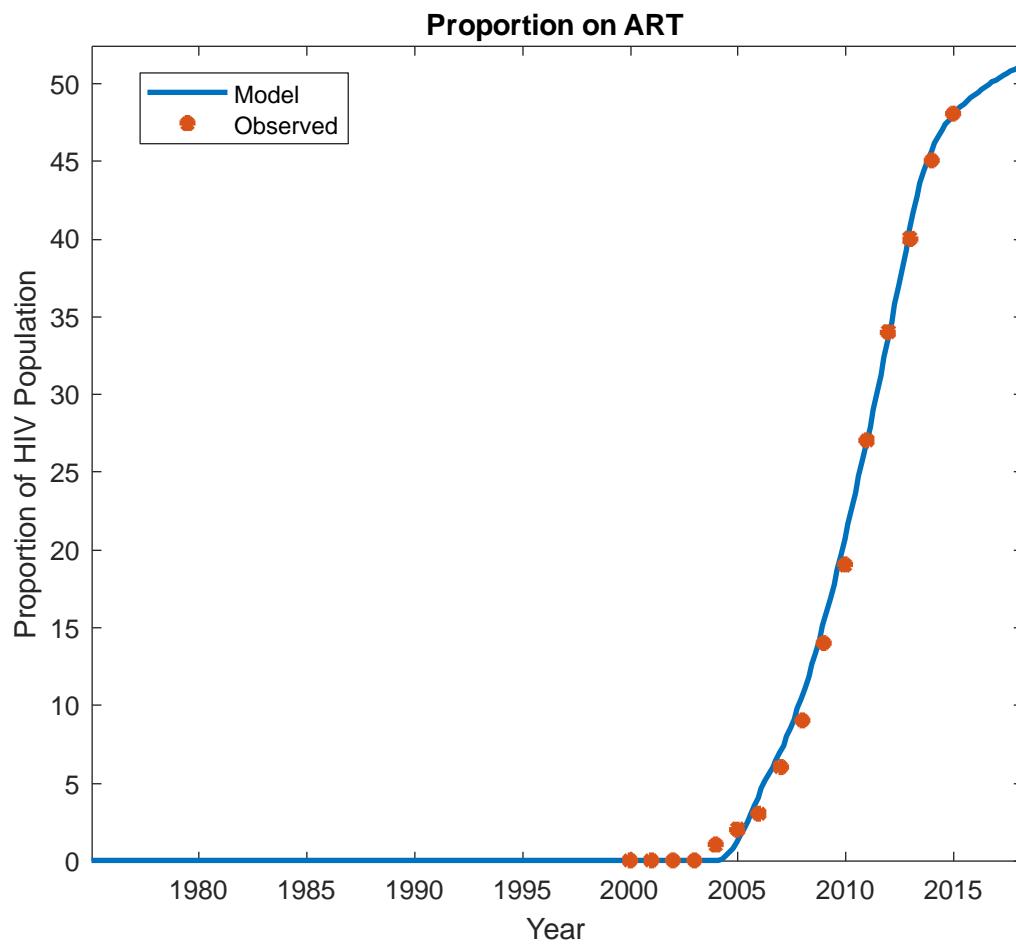




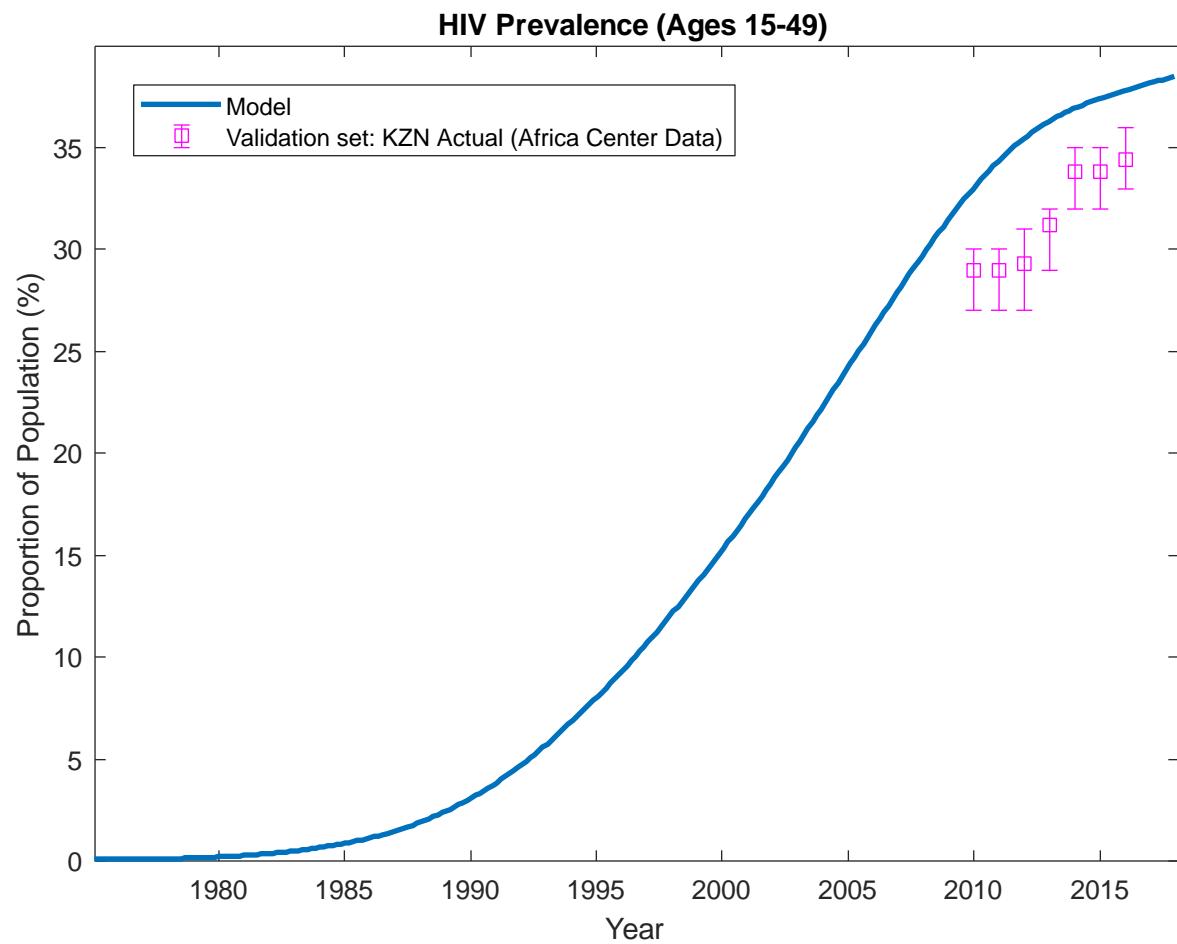


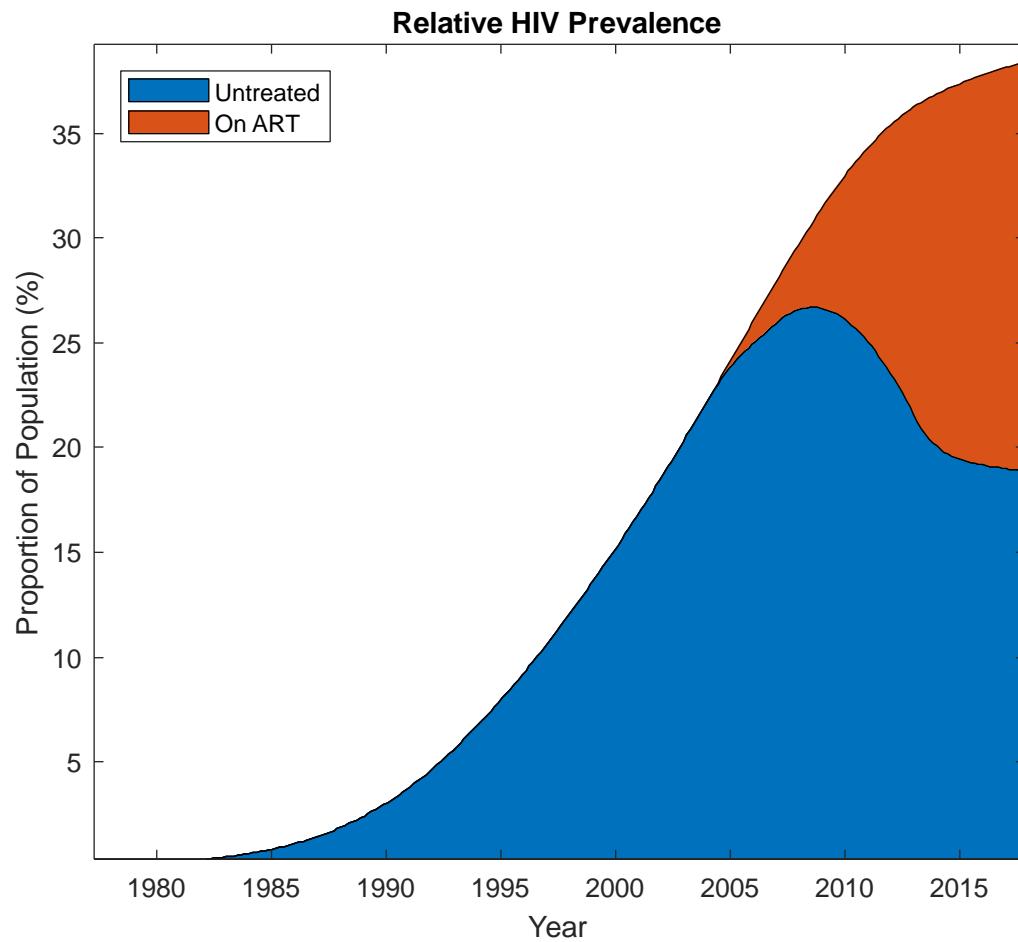




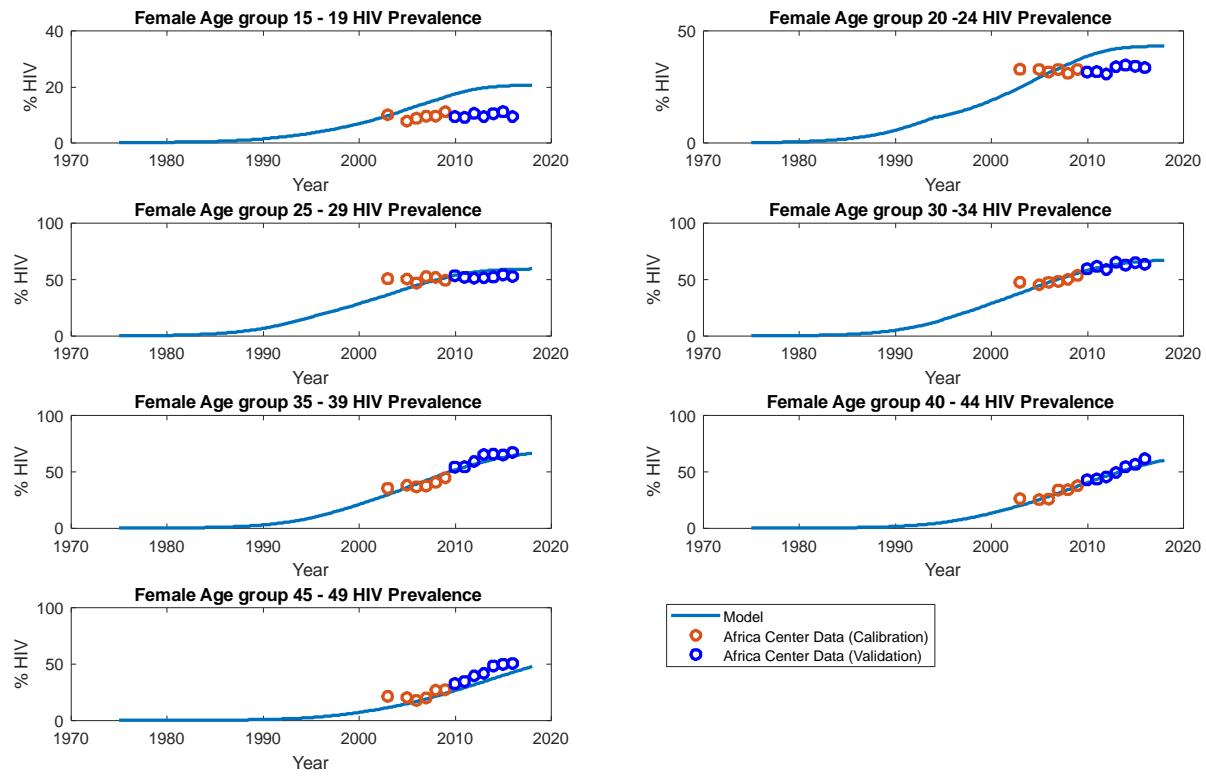


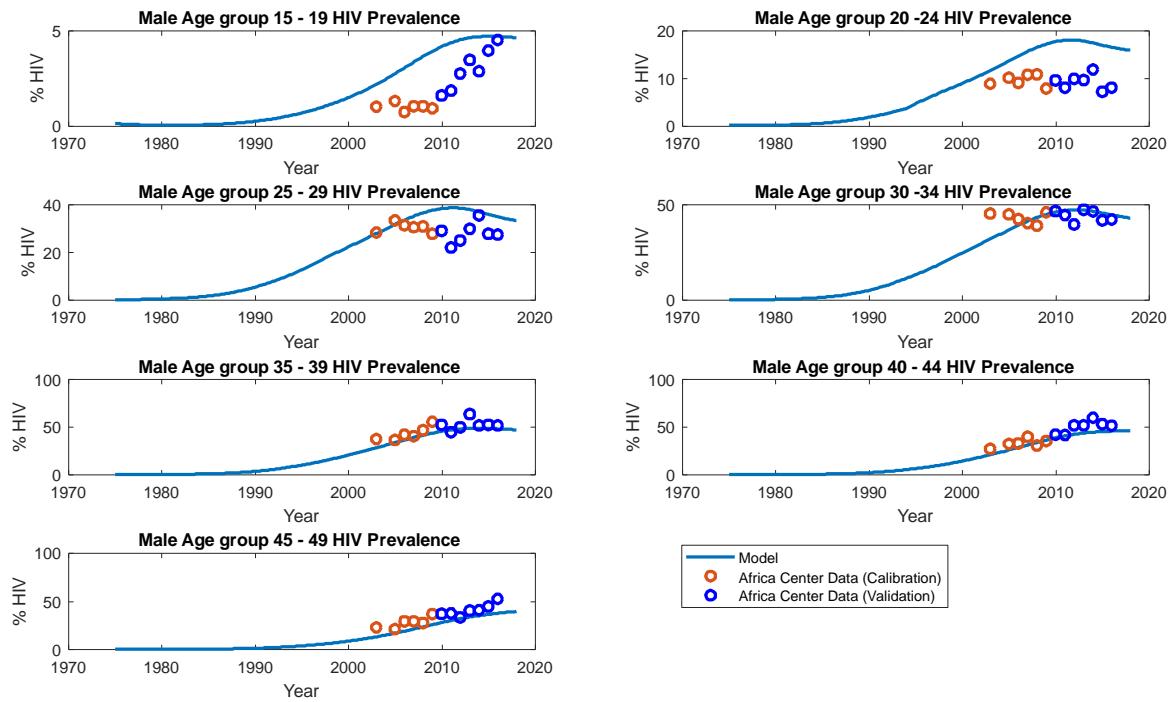
Proportion of all HIV-positive persons on ART in South Africa. Data from World Bank Development Indicators.



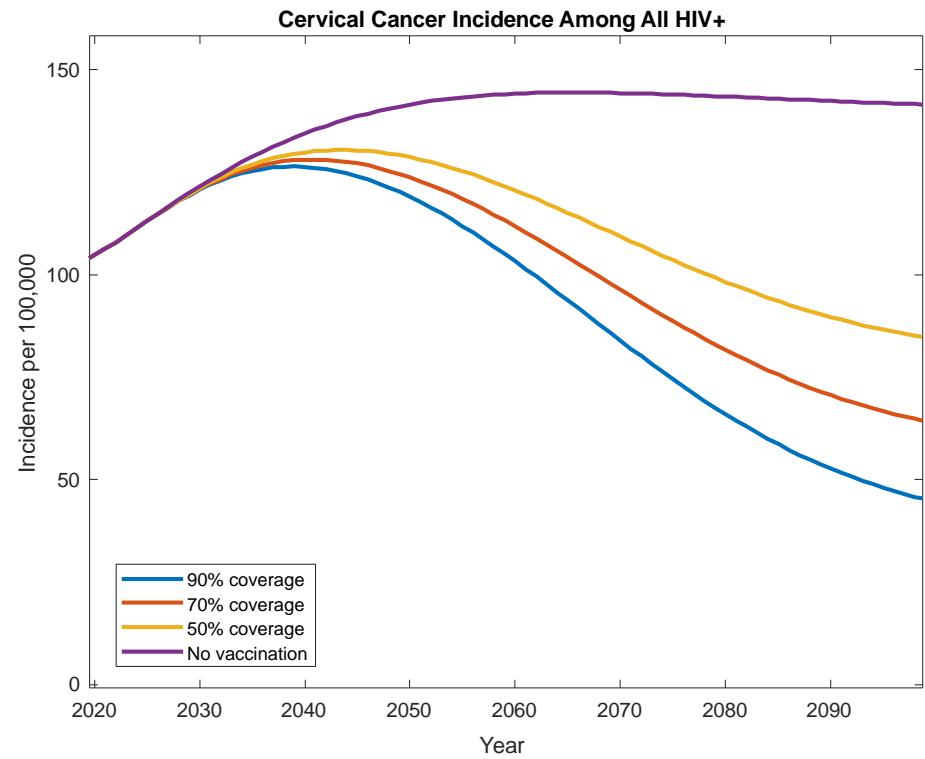
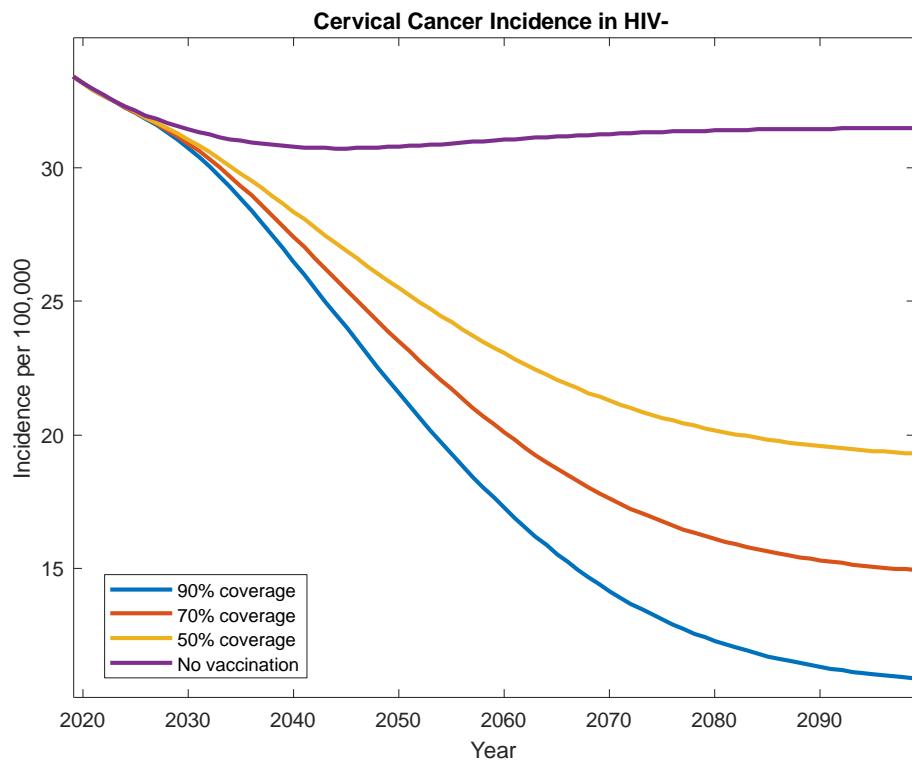


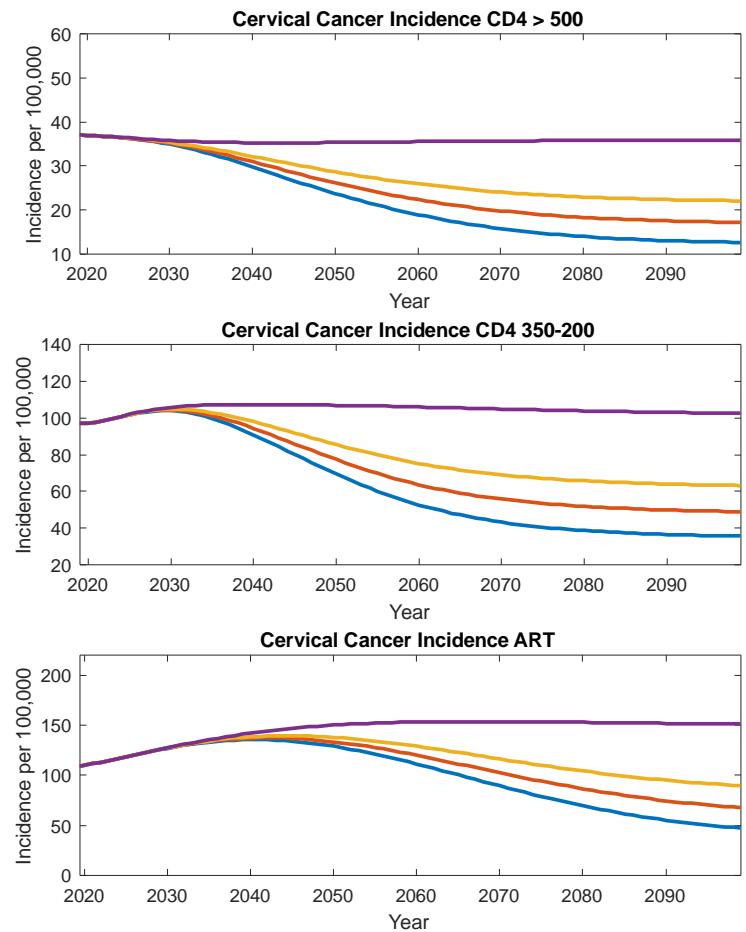
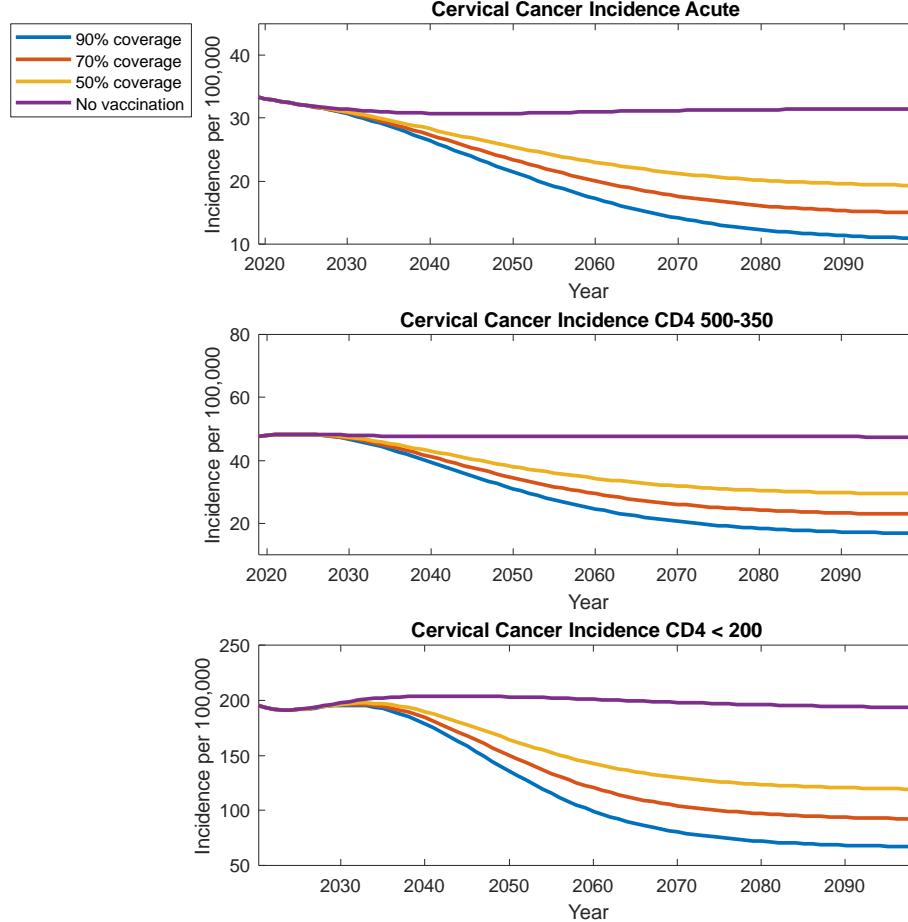
Age and sex-specific HIV prevalence



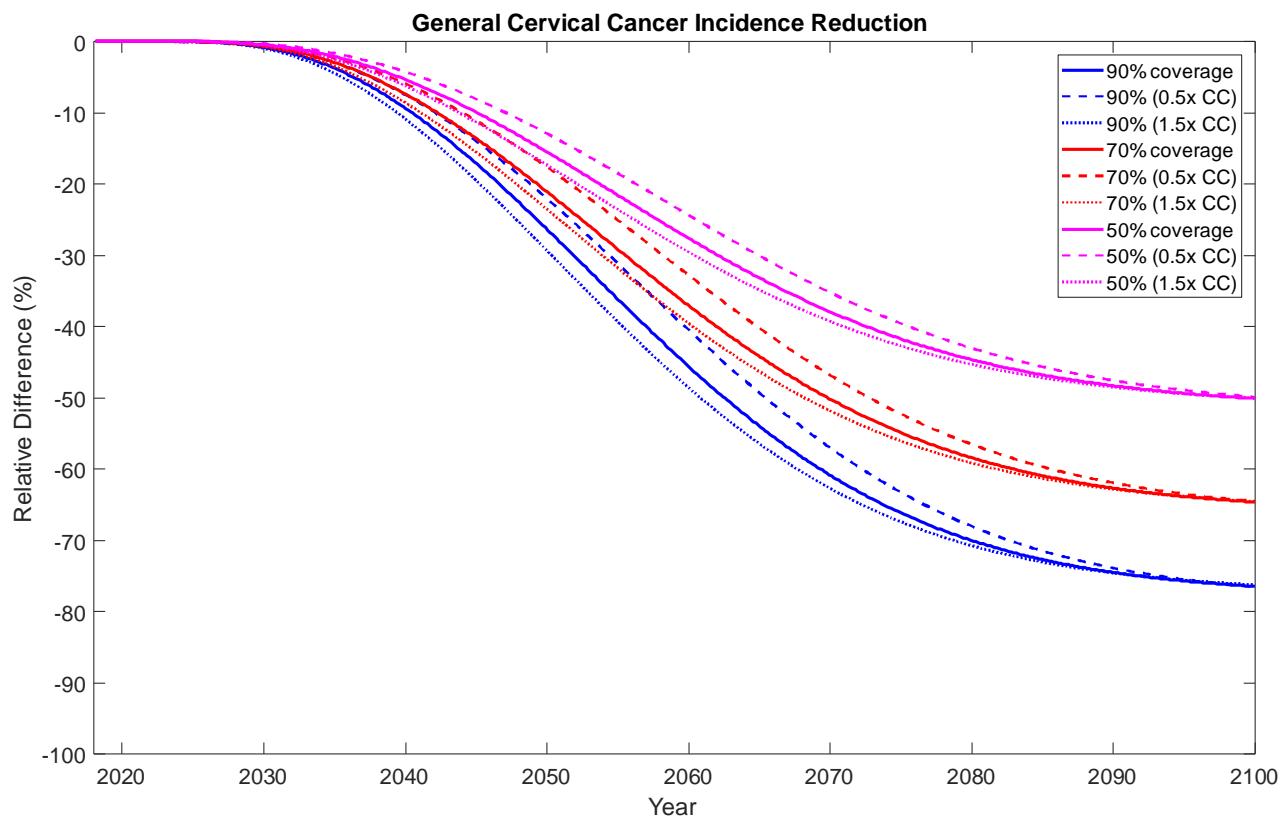


V. Additional Model Outputs

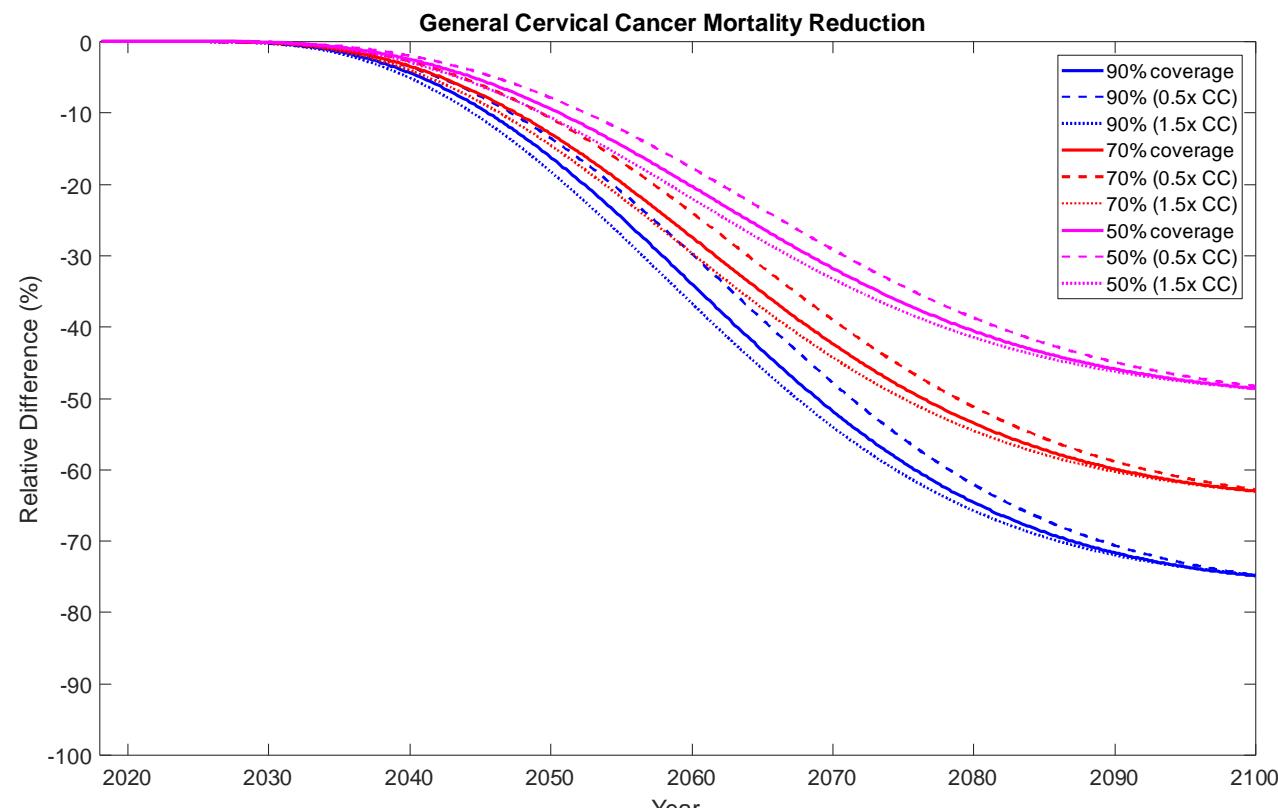




Sensitivity Analysis



Cervical cancer incidence reductions when the transition rate from CIN3 to cervical cancer is varied from 0.5x to 1.5x the base value.



Cervical cancer mortality reductions when the transition rate from CIN3 to cervical cancer is varied from 0.5x to 1.5x the base value.

Table S28. Percent reduction (%) in age-standardized CC incidence 70 years after start of preadolescent 9vHPV vaccination program in KwaZulu-Natal, South Africa with lifelong vaccine efficacy and full protection

Lifelong vaccine protection (varying coverage)	Total female population	HIV-negative females	HIV-positive females on ART	HIV-positive females with CD4>500	HIV-positive females with CD4 350-500	HIV-positive females with CD4 200-350	HIV-positive females with CD4 <200
50%	57	60	56	60	60	59	57
70%	71	75	70	74	74	73	72
90%	82	86	80	85	85	84	83

Table S29. Percent reduction (%) in age-standardized CC mortality 70 years after start of preadolescent 9vHPV vaccination program in KwaZulu-Natal, South Africa with lifelong vaccine efficacy and full protection

Lifelong vaccine protection (varying coverage)	Total female population	HIV-negative females	HIV-positive females on ART	HIV-positive females with CD4>500	HIV-positive females with CD4 350-500	HIV-positive females with CD4 200-350	HIV-positive females with CD4 <200
50%	55	59	52	60	60	59	57
70%	69	73	64	74	74	73	71
90%	80	84	75	85	85	84	82

VI. References

1. International Data Base: South Africa 1985. U.S. Census Bureau.
2. Statistics South Africa. Primary tables KwaZulu-Natal: Census '96 and 2001 compared. . (2004).
3. R. V. Barnabas *et al.*, paper presented at the Treatment as Prevention, Vancouver, Canada, 2012.
4. H. Van Rooyen *et al.*, paper presented at the CROI, Seattle, 2012.
5. R. Bobat, H. Coovadia, A. Coutsdous, D. Moodley, Determinants of mother-to-child transmission of human immunodeficiency virus type 1 infection in a cohort from Durban, South Africa. *Pediatr Infect Dis J* **15**, 604-610 (1996).
6. C. Horwood *et al.*, Elimination of paediatric HIV in KwaZulu-Natal, South Africa: large-scale assessment of interventions for the prevention of mother-to-child transmission. *Bulletin of the World Health Organization* **90**, 168-175 (2012).
7. N. Rollins, K. Little, S. Mzolo, C. Horwood, M. L. Newell, Surveillance of mother-to-child transmission prevention programmes at immunization clinics: the case for universal screening. *AIDS (London, England)* **21**, 1341-1347 (2007).
8. W. H. Adler *et al.*, HIV infection and aging: mechanisms to explain the accelerated rate of progression in the older patient. *Mech Ageing Dev* **96**, 137-155 (1997).
9. E. J. Mills *et al.*, Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. *AIDS (London, England)* **25**, 851-855 (2011).
10. G. P. Garnett, S. Gregson, Monitoring the course of the HIV-1 epidemic: The influence of patterns of fertility on HIV-1 prevalence estimates. *Mathematical Population Studies* **8**, 251-277 (2000).
11. M. Q. Ott, T. Bärnighausen, F. Tanser, M. N. Lurie, M. L. Newell, Age-gaps in sexual partnerships: seeing beyond 'sugar daddies'. *AIDS (London, England)* **25**, 861-863 (2011).
12. R. Anderson, R. May, T. Ng, J. Rowley, Age-Dependent Choice of Sexual Partners and the Transmission Dynamics of HIV in Sub-Saharan Africa. *Phil. Trans. R. Soc. London. B* **336**, 135 - 155 (1992).
13. O. Shisana *et al.*, "South African nation HIV prevalence, incidence, behavior and communication survey 2008: A turning tide among teenagers?", (Cape Town, South Africa, 2008).
14. B. Burington *et al.*, Estimating duration in partnership studies: issues, methods and examples. *Sex Transm Infect* **86**, 84-89 (2010).
15. M. C. Boily *et al.*, Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. *The Lancet infectious diseases* **9**, 118-129 (2009).
16. S. Weller, K. Davis, Condom effectiveness in reducing heterosexual HIV transmission. *The Cochrane database of systematic reviews*, CD003255 (2002).
17. . (KwaZulu-Natal Department of Health, Pietermaritzburg, 2005).
18. S. Attia, M. Egger, M. Müller, M. Zwahlen, N. Low, Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* **23**, 1397-1404 (2009).
19. M. S. Cohen *et al.*, Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **365**, 493-505 (2011).
20. D. Donnell *et al.*, Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* **375**, 2092-2098 (2010).
21. A. Jahn *et al.*, Population-level effect of HIV on adult mortality and early evidence of reversal after introduction of antiretroviral therapy in Malawi. *Lancet* **371**, 1603-1611 (2008).
22. B. Auvert *et al.*, Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS medicine* **2**, e298 (2005).

23. R. H. Gray *et al.*, Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* **369**, 657-666 (2007).
24. H. A. Weiss, M. A. Quigley, R. J. Hayes, Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS (London, England)* **14**, 2361-2370 (2000).
25. T. B. Hallett *et al.*, Understanding the impact of male circumcision interventions on the spread of HIV in southern Africa. *PLoS one* **3**, e2212 (2008).
26. B. G. Williams *et al.*, The potential impact of male circumcision on HIV in Sub-Saharan Africa. *PLoS medicine* **3**, e262 (2006).
27. . (U.S. Census Bureau).
28. . (2004).
29. S. Moyo *et al.*, Analysis of Viral Diversity in Relation to the Recency of HIV-1C Infection in Botswana. *PLoS one* **11**, e0160649 (2016).
30. . (World Health Organization, Geneva).
31. . (United Nations Children's Education Fund).
32. A. Ross *et al.*, HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. *AIDS (London, England)* **18**, 799-804 (2004).
33. M. L. Newell *et al.*, Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet* **364**, 1236-1243 (2004).
34. M. Badri, S. D. Lawn, R. Wood, Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study. *Lancet* **368**, 1254-1259 (2006).
35. T. C. Quinn *et al.*, Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* **342**, 921-929 (2000).
36. G. Abongomera *et al.*, Population level usage of health services, and HIV testing and care, prior to decentralization of antiretroviral therapy in Agago District in rural Northern Uganda. *BMC health services research* **15**, 527 (2015).
37. F. Tanser *et al.*, Cohort Profile: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. *Int J Epidemiol* **37**, 956-962 (2008).
38. L. Ahdieh *et al.*, Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis* **184**, 682-690 (2001).
39. Z. Z. Mbulawa, D. Coetzee, A. L. Williamson, Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. *BMC Infect Dis* **15**, 459 (2015).
40. R. Sankaranarayanan *et al.*, Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* **370**, 398-406 (2007).
41. S. Dryden-Peterson *et al.*, HIV Infection and Survival Among Women With Cervical Cancer. *J Clin Oncol*, (2016).
42. B. Allan, D. J. Marais, M. Hoffman, S. Shapiro, A. L. Williamson, Cervical human papillomavirus (HPV) infection in South African women: implications for HPV screening and vaccine strategies. *J Clin Microbiol* **46**, 740-742 (2008).
43. A. C. McDonald *et al.*, Distribution of high-risk human papillomavirus genotypes among HIV-negative women with and without cervical intraepithelial neoplasia in South Africa. *PLoS One* **7**, e44332 (2012).
44. P. Schuman *et al.*, Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis* **188**, 128-136 (2003).

45. H. C. Johnson, K. M. Elfström, W. J. Edmunds, Inference of type-specific HPV transmissibility, progression and clearance rates: a mathematical modelling approach. *PLoS One* **7**, e49614 (2012).